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TABLE OF CONTENTS

The Dormant Cancer Cell GEOFFREY HADFIELD, M.D., F.R.C.P. 607
Influence of Excess Vitamin A on the Sulphate Metabolism of Chick Ectoderm Grown in Vitro H. B. FELL, D.SC., F.R.S., Sir EDWARD MELLANBY, G.B.E., K.C.B., F.R.S., and S. R. PELC, D.Phil. 611
Thrombotic Thrombocytopenic Purpura D. J. ELLISON, M.B., M.R.C.P.Ed., and O. C. LLOYD, M.D. 612
Galactosaemia P. J. N. COX, B.M., M.R.C.P., D.C.H., and R. J. P. PUGH, M.B., M.R.C.P., D.C.H. 613
Congenital Galactosaemia M. W. ARTHURTON, M.D., M.R.C.P., D.C.H., and B. W. MEADE, M.D. 618
Operative Cholangiography E. S. R. HUGHES, M.S., F.R.C.S., F.R.A.C.S., and R. H. KERNUTT, M.S., F.R.A.C.S. 620
Pathological Changes in the Liver in Salm. Typhi-murium Infection E. J. S. WOOLLEY, M.R.C.P. 623
Primidone in the Treatment of Epilepsy J. B. LYONS, M.D., M.R.C.P.I., and L. A. LIVERSEDGE, M.D., M.R.C.P. 625
Primidone in Mental Deficiency Practice D. S. SHARPE, M.R.C.S., L.R.C.P., D.P.M. 627
Use of Polymyxin B in the External Ear D. A. T. FARRAR, M.B., F.R.C.S. 629

MEDICAL MEMORANDA

Sickling and Malaria. R. A. MOORE, L.R.C.P.&S.I., D.T.M.&H., W. BRASS, B.SC., and HENRY FOY, Ph.D., D.SC. 630
Superior Sulcus Tumour. R. D. YOUNG, M.B., M.R.C.P.Ed. 631
Asthma Induced by Antihistamines. D. B. MACAULAY, M.B., M.R.C.P. 632
Optimum Injection Volume for Intramuscular Streptomycin Sulphate. PETER STRADLING, M.D., M.R.C.P., and L. C. KREEGER, M.B. 632
Metastases from Carcinoma of Bronchus causing Enormous Enlargement of Liver R. A. McINROY, M.B., D.T.M.&H. 633

BOOK REVIEWS 634

GENERAL ARTICLES AND NEWS

British Association 641
MENTAL HEALTH AND PUBLIC AFFAIRS 642
PREPARATIONS AND APPLIANCES 643
NOVA ET VETERA 643
UNIVERSITIES AND COLLEGES 653
MEDICAL NEWS 655
BIRTHS, MARRIAGES, AND DEATHS 656
QUESTIONS AND COMMENTS 657

Vital Statistics 654

LEADING ARTICLES

Dormancy in Cancer 635
Antibiotics and Growth 635
Radiological Examination of the Bile Passages 636

ANNOTATIONS

Cancer Cells in Diagnosis of Poliomyelitis 638
Fluoridation in Britain 638
Family Service Units 639
Galactosaemia 640
Midwives International Congress 640

CORRESPONDENCE

Blood Groups and Disease. T. M. ALLAN, M.B. 644
Physique and Performance. W. DYKES BOWER, M.R.C.P.; R. L. SIKES, M.R.C.S. 644

SUPPLEMENT

Full Contents on First Page of Supplement
The Forces Medical and Dental Services Committee 111
Medical Practices Committee (England and Wales) 113
Correspondence:
Drugs for Private Patients. O. C. CARTER, M.B. 116
Private Patient in General Practice. J. TORLEY, M.B. 116

CORRESPONDENCE—*cont.*

Smoking and Cancer. T. L. CLEAVE, M.R.C.P. 645
Infant-feeding. R. A. DE K. GLOVER, M.R.C.S. 645
Explosions of Bowel Gas. A. H. GALLEY, M.B., F.F.A. R.C.S. 645
Tooth-protector for Laryngoscope. R. BLAIR GOULD, F.F.A. R.C.S.; A. S. GARDINER, B.M. 645
Pitocin in Obstetrics. M. LESSER, M.B., D.Obst.R.C.O.G. 646
Plastic Surgical Dressing. S. A. LEADER, M.R.C.S. 646
Drainage in Mastectomy. J. JEMSON, F.R.C.S. 646
Actinomycosis. J. A. ROSS, F.R.C.P.Ed., and I. C. S. KNIGHT, F.R.C.S.Ed. 646
Cerebrospinal Fluid Sugar in Tuberculous Meningitis. J. G. ALEXANDER, M.D. ..646
Letters on other subjects appear on p. 647

OBITUARY

Alfred Cox, O.B.E., M.A., LL.D., M.B. 648
B. T. Parsons-Smith, M.D., F.R.C.P. 649
F. C. Bottomley, O.B.E., M.D. 650
G. W. Will, O.B.E., M.B. 650
H. F. Lechmere Taylor, M.D., D.P.H. 651
C. U. Whitney, M.R.C.S. 651
J. W. Fisher, Ph.D., M.R.C.S. 651
Duncan McLellan, M.D. 652
F. E. Preston, L.R.C.P.I., D.O.M.S. 652
H. W. Bowyer, M.D. 652
W. W. McGrath, M.B. 653

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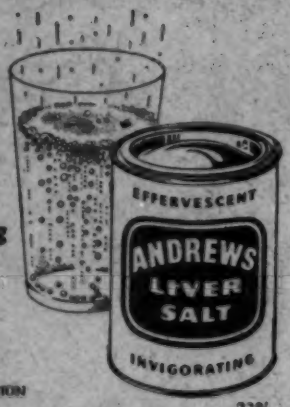

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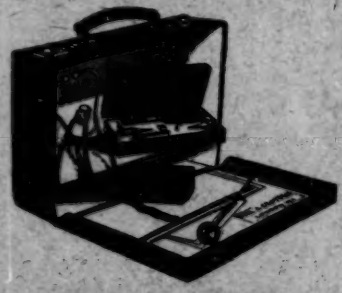

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 11 1954

THE DORMANT CANCER CELL*

BY

GEOFFREY HADFIELD, M.D., F.R.C.P.

Sir William Collins Professor of Pathology and Dean of the Institute of Basic Medical Sciences, Royal College of Surgeons of England

[WITH SPECIAL PLATE]

The time elapsing between the excision of a human malignant tumour and the appearance of a clinically recognizable recurrence varies from a few months to thirty years. It is usually short, being less, sometimes appreciably less, than a year or so, and when of this order of duration it is probable that the secondary tumours are the product of continuous and unsuppressed proliferation of the cells of microscopic fragments of growth, some of which are portions of the primary growth which have escaped excision, whilst others had already reached a distant organ or tissue by lymphatic, venous, or arterial embolization before the tumour was removed.

Temporary Mitotic Arrest

When the interval between excision and the appearance of secondary tumours exceeds two and reaches four or more years, it becomes increasingly difficult to believe that cellular proliferation in the residual tumour fragments has been continuous and uninhibited. We cannot, for instance, assume that these longer intervals are characteristic of slowly growing tumours, because remarkably long intervals have often been described in tumours whose original and subsequent rates of growth were very rapid. When the interval is prolonged to six years or more it seems impossible to escape the conclusion that the cells of the dormant growth are in a state of *temporary mitotic arrest*, no matter how long the period may b. This conclusion becomes all the more probable when we witness the clinical resurrection of these minute foci of dormant cancer cells after a long period of latency and satisfy ourselves that they have lost none of their former capacity to grow rapidly and infiltrate widely.

In cancer literature there are many accounts of instances in which the clinically silent periods of mitotic arrest have been remarkably long, and the following table is a summary of some of these reports gathered together by Willis (1948).

Site	Latent Period
Breast (carcinoma)	6 to 20 years
Cutaneous and ocular melanoma ..	14 to 32 ,,
Kidney (carcinoma)	6 to 8 ,,
Tongue (carcinoma)	8 to 15 ,,
Stomach and colon (carcinoma) ..	5 to 6 ,,

Long latent periods of this order are certainly uncommon in the natural history of malignant disease. The usual course, although often punctuated by short intermissions, is one of continuous cellular proliferation and progressive clinical deterioration, its length being primarily determined by the average growth rate of the tumour cells.

Instances in which the clinical course shows an uncommonly long period of mitotic arrest seem to be reported in cancer literature only when the latent period ending in recurrence is exceptionally long. In one sense this practice is misleading, for periods varying from three to six years are far from exceptional in the natural history of malignant tumours, and I find it difficult to escape the conclusion that during periods of this duration the tumour cells are in the same state of mitotic arrest as they almost certainly are when the period is exceptionally long.

In any case, the phenomenon of temporary growth suppression in tumour pathology is of obvious biological importance, and for the sake of brevity in choosing a title for this lecture I have used the word "dormant" to describe malignant cells which, although remaining alive in the tissues for relatively long periods, show no evidence of multiplication during this time, yet retain all their former and vigorous capacity to multiply.

Anatomical Site of Dormant Growths

Local Recurrence

There are three situations in which such dormant cancer cells may exist. Some lie in or near the operation site, where it is highly probable that they are involved in post-operative scar. When they eventually recur they produce secondary growths which not infrequently lie in close relationship with the skin incision or its deep extensions. Here they exist for long periods of time in poorly vascularized mature collagenous connective tissue, an environment which possibly subjects them to long periods of relative anoxia. Other foci of dormant growth may lie in regional lymph nodes, where in some growths, especially those of the breast, they may again survive but fail to multiply in a fibrous and possibly anoxic environment. It may not be unreasonable to assume, therefore, that in these situations mitotic arrest has been induced by anoxia or some similar and closely related metabolic deficiency, and, alternatively, that mitosis would be re-established if adequate oxygen became available by vascularization of the scar, an event which may be brought about by an inflammatory response to one or more of many varieties of local injury, possibly including irradiation.

Metastatic Growth

On the other hand, we have no information which might help us to understand the induction of the dormant state and the reactivation of microscopic foci of metastatic tumour tissue in deeply placed organs. Such foci must have been originally implanted before excision of the primary growth. In all probability they were small enough to have arisen

*Kettle Memorial Lecture delivered at the Royal College of Surgeons of England on December 14, 1953.

as the result of malignant embolism of small arteries and arterioles, and if these emboli were impacted in the systemic arterial circulation the tumour fragments must have either directly traversed the lung capillaries or have broken away from a far larger pulmonary venous metastasis which itself becomes dormant. The first of these alternatives would appear to be far the more probable.

The anatomical site of these minute quiescent growths must be significant, for in at least 50% of cases of malignant disease recurring after latent periods varying from five to thirty years reactivated metastatic growth of macroscopic size was found in the haemopoietic bone marrow. In 1912, E. H. Kettle, to whose memory this lecture is dedicated, drew attention to the presence of microscopic foci of metastatic carcinoma in the pulp of the normal-looking unenlarged spleen. He proposed that such growths lying in the territory of the portal vein may be the source of hepatic metastases when the primary growth lies outside the portal area.

More recently, Clifton and his co-workers (1952) have reported that in 33% of a series of 57 cases of carcinoma of the prostate carcinoma cells were demonstrated in the sternal bone marrow. The cells occurred with equal frequency in marrow from the sternum and ilium, and in 9% there was widespread skeletal dissemination of growth with no diagnostic evidence other than that provided by the marrow biopsy. Evidence of this sort provides the hint that during the period of blood-borne invasion of the systemic organs by tumour cells malignant emboli tend to occur in organs such as those of the reticulo-endothelial system, the hypophysis, and the adrenal cortex, all of which have a sinusoidal capillary circulation. I have a strong impression that the phenomenon of mitotic arrest for long periods is rare in the kidney, lung, brain, and skeletal muscle. On the other hand, there seems to be little doubt that unsuspected microscopic metastases may not infrequently be present in the adrenal cortex, at least in carcinoma of the breast. I have personally seen, or have had reported to me by competent observers during the last 18 months, at least seven instances in which such metastases have been found in surgically excised adrenal glands which are neither enlarged nor deformed. During this period similar latent metastases have been observed in five surgically removed normal-looking ovaries in patients suffering from the same disease.

However suggestive these observations may be, it must be conceded that our present clinical and pathological knowledge of human tumour pathology provides us with no reliable information regarding the environmental factors which induce mitotic arrest of tumour cells in human tissues for periods varying from three to thirty years, and it seems improbable that morphological and histological studies will ever do so. We must inquire, therefore, if fundamental cancer research can or is likely to help our understanding of this remarkable phenomenon.

Experimental Induction of Dormant State

I would suggest that the investigations which have grown out of studies on the low-temperature preservation of animal tumours might supply us with relevant information. The cells of certain normal tissues and those of some malignant tumours show remarkable powers of survival after long periods of freezing to and below −70° C. Michaelis (1905) demonstrated that the cells of the Jensen carcinoma were still viable and would produce tumours in animals after exposure to liquid air for 30 minutes. Shortly afterwards Paul Ehrlich (1907) found that several malignant tumours in animals survived temperatures between −25° C. and −30° C. for 48 hours, and one tumour kept at −8° C. to −10° C. was still viable after two years.

Several observers (Cramer, 1930; Auler, 1932; Klinke, 1939) confirmed these early observations. Barnes and Furth (1937) made the important observation that the survival rate of frozen tumour cells was higher if the tumour was frozen slowly, and Breedis and Furth (1938), using sarcomata and the tumour tissue of fowl leukaemia, demonstrated tumour survival for 430 to 448 days at a temperature of −70° C. An animal carcinoma mammae was still viable after 98 days. They were satisfied that their results were due to survival of tumour cells as opposed to a virus or virus-like agent, for after irradiation of the frozen tumour at an intensity which was lethal to its cells but was considered to be non-lethal to any known virus particles their tumours failed to grow on homologous transplantation. The hypothesis that freezing kills tumour cells but spares virus was postulated by Gye (1949) and supported by Mann and Dunn (1949). It was asserted by Craigie that a survival rate, after freezing, of one in a million cells was sufficient to propagate a tumour, while Passey and Dmochowski (1950) demonstrated, by using tissue culture as a test of viability, that transmission was due to cell survival. They also demonstrated that the cell-free supernatant of a centrifugalized thawed-out tumour suspension was incapable of transmitting the tumour, whilst the cellular deposit did so with ease.

The Trauma of Freezing

The therapeutic use, after long periods of preservation in the frozen state, of red blood cells, spermatozoa, bone, skin, and other tissue grafts, as well as large arterial trunks, has called for detailed investigation into the physico-chemical factors involved. Luyet and Gehenio (1940) and Luyet (1951) made the assumption that trauma to cell and nuclear membranes inflicted by ice crystals is a major lethal factor when cells are exposed to low temperatures, possibly because laceration of either membrane would allow nuclear or cytoplasmic material to escape. They decided that cooling and thawing must be carried out so rapidly that the cell contents undergo non-crystalline, amorphous consolidation or *vitrification*.

The conditions governing this ideal physical transformation are that the rate of cooling must be of the order of several hundred degrees per second to a temperature of −40° C., the thickness of the material less than 0.1 mm., and its water content less than 70%. These conditions appear to be impossible of practical achievement when dealing with tumour material whose viability must be subsequently determined by grafting. Furthermore, in the case of tumour tissue, a significantly higher survival rate is obtained by slow freezing and rapid thawing than the reverse (Breedis, Barnes, and Furth, 1937; Breedis and Furth, 1938; Craigie, 1949a, 1949b, 1949c, 1954). It is quite conceivable that slow freezing enables tumour cells to effect certain physico-chemical and structural adjustments which seem to be essential if they are to resist anoxia and dehydration. It appears, therefore, that the vitrification hypothesis may not be applicable to tumour cells and the lacerating trauma inflicted on cell membranes by ice crystals is not so lethal a factor as was once thought.

Dehydration at Low Temperatures

It is, in fact, becoming increasingly probable that one of the major factors in the trauma produced by freezing is the inevitable loss of cell water by simple exosmosis, which is clearly due to the development of a hypertonic concentration of inorganic ions in the extracellular fluid as its water crystallizes. For example, a solution of sodium chloride having a concentration of 0.85% at 15° C. reaches a concentration of 30% at −18° C.

Whilst the capacity of a frozen cell to withstand the physico-chemical effects of cold appears to decide whether it shall survive or perish, experimental evidence strongly suggests that a certain sublethal degree of dehydration is an essential prerequisite for survival. It has been shown that extreme degrees of dehydration can be avoided and an optimal degree established by eliminating electrolytes from the fluid in which the tumour cells are suspended, and substituting for them a soluble non-electrolyte. Glycerol has been extensively used for this purpose, and Craigie (1949a, 1949b, 1949c) has successfully employed solutions of glucose

in which the tumour cells are preconditioned before freezing. This, he finds, affords excellent protection for tumour cells against the physical hazards of freezing in slightly hypertonic concentrations of between 6 and 7%. When tumour cells are preconditioned in this way, slowly frozen at −70° C. or lower, stored at this temperature, rapidly thawed, and immediately examined, all the surviving and viable cells are found to be spherical in shape and to have suffered a significant reduction in volume, which rapidly increases to normal as the temperature rises. Using this technique, Craigie (1954) demonstrated that S 37, a highly malignant sarcoma of mice, was still viable and highly malignant after continuous storage at −70° C. for three years and seven months; the Daels guinea-pig tumour, a sarcoma originally induced by radium, survived for two years and five months, and the Walker rat sarcoma for one year and nine months. Neither of these tumours had lost its former capacity to grow rapidly and metastasize widely.

Growth in Peritoneal Cavity

When subjecting malignant tumours to low temperatures it is obviously desirable that they should be first reduced to a homogeneous suspension of single living cells in a suitable fluid. If this is attempted by the usual technique of mincing the solid tumour, a high proportion of its cells are killed and their autolytic products are certainly toxic to the cells which survive. This can be avoided by using the familiar *ascites tumour*, whose cells grow freely in a peritoneal exudate. Craigie (1953) has shown that certain solid mouse sarcomata can be forcibly converted to ascites tumours by intraperitoneal inoculation, and when so converted can be readily propagated as ascites tumours. Tumour cells grown in this way show a high rate of survival when frozen, and this is largely due to eliminating the trauma of "mincing."

Resistance of Normal Cells to Low Temperatures

The ability to survive in a frozen environment without any loss of former reproductive power is a property which the cells of some malignant tumours share with certain normal cells. Breedis and Furth (1938) demonstrated survival of tracheal epithelium after freezing for 327 days; Mider and Morton (1939) successfully grafted rat skin after prolonged freezing at −74° C. Webster (1944) proved that human skin grafts were viable after refrigeration at −72° C. Strumia and Hodge (1945), using autogenous split-thickness grafts of human skin, demonstrated survival after 1 to 61 days at −20° C. to −25° C. They obtained 80% of permanent "takes" with 41 frozen grafts, against 86% in unfrozen controls. Blumenthal and Walsh (1950) showed that thyroid and parathyroid epithelium were viable after freezing at −75° C. Similar results were obtained with ovarian granulosa cells of the rabbit (Smith, 1952), rat ovarian tissue (Parkes and Smith, 1953), and Malpighian cells and epidermal melanoblasts (Billingham and Medawar, 1951). Spermatozoa are highly resistant to freezing. Macrophages and other mesenchymal elements frozen with tumour tissue survive for long periods (Craigie, 1954).

Morphological Changes

Exposure to low temperatures induces a series of remarkably interesting morphological changes in the cells of several malignant tumours which after suspension in 6.5% glucose, followed by slow freezing, are able to survive low temperatures for long periods. These have been studied by Craigie and described in a series of papers (Craigie, 1950, 1952a, 1952b, 1952c, 1954).

The Paramorphic Cell

If tumours which have been maintained at −70° C. for many months are rapidly thawed and quickly examined, cells possessing clearly defined nuclei may be seen which from their appearance show little obvious abnormality and are often partially differentiated. Craigie asserts that these cells are dead, disintegrate at 37° C., and are incapable of transmitting the tumour on grafting. In addition to these, a very variable number of smaller and highly refractile spherical bodies are seen in which no nuclei are visible, and whose plasma membrane is highly refractile and appears to be thickened (see Plate, Fig. 1). Craigie at first thought that these "spherical bodies" were dead cells, but when suspended in oxygenated Tyrode solution at 37° C. they become hydrated, and by throwing out pseudopodia and becoming mobile declare themselves as living cells. The invisibility of their nuclei may be the result of the inevitable loss of nuclear water during freezing, the nuclear refractive index closely approaching that of the surrounding cytoplasm. The refractile and apparently thickened plasma membrane is revealed by phase-contrast microscopy to be an optical artifact due to the formation of a bright light halo which invests the cell externally and intervenes between the plasma membrane and the cytoplasm internally (Fig. 1).

It is probably highly significant that these cells show intense absorption of ultra-violet light at 2,536 A, so that when photographed at this wavelength the light absorption is so great that their photographic image is almost black. It is reasonably certain that this phenomenon indicates a heavy intracellular concentration of cytoplasmic pentose-nucleic acid and is possibly due to loss of cell water. It may be that this heavy concentration of large intracellular molecules acts as a biological "anti-freeze" mixture which prevents the crystallization of residual cell water. In any case, it seems safe to assume that an optimal degree of intracellular dehydration is an essential prerequisite for cell survival.

Craigie describes this small spherical refractile cell as "paramorphic," and, whilst the reasons given for its peculiar morphology are to some extent speculative, there is little, if any, doubt that of all the varied cell types present in a malignant tumour the capacity to resist and survive anoxia, dehydration, and metabolic arrest is strictly limited to the paramorphic cells it contains. This belief rests on the demonstration that *the tumour-inducing activity of a thawed-out malignant tumour after a long period of anoxia is directly related to the number of paramorphic cells present in it.*

At 37° C., under isotonic conditions and access to free oxygen, the paramorphic cell increases in volume, becomes mobile, and its refractility lessens. If frozen in this phase it may again lose volume and assume the characters of the resistant paramorphic cell. If kept at 37° C. refractility disappears, the nucleus becomes visible, mobility is lost, and the degree of absorption of ultra-violet light progressively falls. If frozen in this phase reversion to the paramorphic state is improbable. If kept at 37° C. with ample available oxygen, differentiation of structure begins and the cell becomes capable of mitosis (see Plate, Fig. 2), but if exposed to low temperatures in this phase reversion to the paramorphic state is extremely unlikely and in all probability impossible.

Experimental conditions which govern the induction of the paramorphic state in the cells of malignant tumours, and the biological significance of the morphological changes described, need confirmation and amplification, but within these limitations it may be permissible to make the following generalizations:

1. When defended against the harmful physical effects of cold the cells of some malignant tumours have a remarkable capacity to survive the anoxia and metabolic arrest induced by exposure to low temperatures *in vitro*.

2. After long periods in the frozen state certain cells in these tumours retain their full reproductive vigour and malignant potentialities when grown in tissue culture or transplanted into the tissues of animals of the same species.

3. The capacity of a frozen tumour to survive appears to be strictly limited to its undifferentiated cells.

4. These cells share this attribute with certain cells of normal tissues.

5. Tumour cells capable of surviving undergo rapidly a series of characteristic morphological changes when subjected to low temperatures.

6. Some or all of these morphological changes may be the direct consequence of the operation of purely physical factors, such as dehydration. On the other hand, the ability of a tumour cell to undergo these modifications of structure appears to decide if the cell shall survive or perish in an anoxic environment, and if it survives whether it shall retain its former capacity to multiply and to initiate a race of cells which infiltrate and metastasize in the tissues of an animal of the same species as the original host.

At the beginning of this lecture I described the naturally occurring phenomenon of total mitotic arrest in human malignant tumours. On the evidence provided by our knowledge of human tumour pathology this phenomenon seems to fall within the category of unsolved and insoluble biological mysteries. I now invite you to consider whether the experimental induction *in vitro* of a dormant state in tumour cells may be germane to this problem. Your first reaction to this suggestion is likely to be unsympathetic. You may regard the changes which take place in frozen tumour cells as being part of a strictly specific reaction to cold. You may look upon any comparison between the human cancer cells becoming "dormant" at body temperature and the animal tumour cell becoming "paramorphic" at −70° C. as being so strained and artificial that it hardly merits serious consideration.

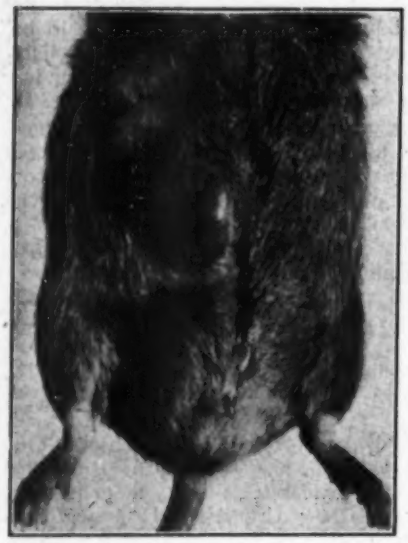

FIG. A.—Tumour mass in mouse six days after grafting cells of a benzpyrene-induced sarcoma which had been kept at −70° C. for nearly five years.

May I remind you that tumour cells have been kept alive in a frozen and anoxic state for periods of time which are obviously comparable to those during which tumour cells remain temporarily dormant in human tissues, that this has been achieved by deliberately defending them against the lethal physical effects of cold, and that such cells emerge from the frozen state with no apparent deterioration in their biological or malignant characteristics? I would therefore like to suggest that when the preconditioned tumour cell is very cautiously frozen it suffers no permanent injury, and that the only demonstrable effect of a cold environment upon it is temporarily to inhibit its intracellular enzyme systems without any impairment of their potential efficiency.

If these suppositions prove to be true, and they certainly need confirmation, the experimentally produced paramorphic tumour cells of transplantable animal cancer can be regarded as existing in a biological state closely related to, or possibly identical with, the naturally occurring "dormant cancer cells" of human pathology. By investigating the paramorphic cell we may therefore learn something of the biological state in which these dormant cells survive in human tissues before they begin to proliferate.

The fact that malignant cells can be induced to survive long periods of experimental metabolic arrest would appear to offer an explanation of their *in vivo* ability to withstand separation from their parent growth until a capillary circulation is provided for them. This may well apply to the microscopic foci of isolated cells which form the nucleus of a metastasis, or to groups of cells of comparable size which become completely detached from their parent growth during the process of malignant infiltration. In conclusion, I would like to claim that the preconditioning techniques employed to obtain maximum survival of cells in the frozen state provide us with a valuable experimental method which, without inflicting any permanent cytological injury, enables us temporarily to suppress the metabolic activities of the cells of malignant tumours.

ADDENDUM

Since this lecture was delivered, another series of malignant tumours, stored at or below −70° C. for a remarkably long period, have been thawed out and tested for viability. I am permitted by Dr. J. Craigie, Director of the Imperial Cancer Research Fund's Laboratories at Mill Hill, to report the following details concerning them:

A Fresh Series

There are six sarcomatous tumours in this series.

They were originally induced by the subcutaneous injection of benzpyrene into mice. All were found to be transmissible by grafting and all were sarcomatous, but each of them differed significantly from the others in cytological structure.

The cells of these tumours were suspended in dextrose and frozen at −70° C. on April 12, 1949. They remained undisturbed at this temperature until February 8, 1954—a period of 4 years 9 months 27 days. They were then thawed out and grafted into mice.

All the tumours grew vigorously (see Fig. A and Plate, Fig. 3) and had suffered no loss of viability while frozen, for they became visible to the naked eye after a substantially shorter period than those produced in animals of a control series.

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War injuries are far from being the principal cause of amputations, according to reports submitted to the World Health Organization for a conference on prosthetics held in Copenhagen last month. In the United States, for instance, the second world war produced 18,000 amputees in the armed Forces; during the same period, automobile and industrial accidents, disease, and congenital deformity produced 120,000 civilian amputees. In England, since the war, an average of 3,000 to 4,000 new cases of amputation come forward each year to be fitted with new limbs; in Germany, between 7,000 and 8,000. However, for most countries in the world, the size of the problem is unknown. The aim of the conference was to evolve plans for the organization of prosthetic services in countries with growing industrial and transportation facilities.

G. HADFIELD: THE DORMANT CANCER CELL

FIG. 1.—Cell of a benzpyrene-induced mouse sarcoma which survived many months at −70° C. in the paramorphic state. As seen by phase contrast soon after thawing.

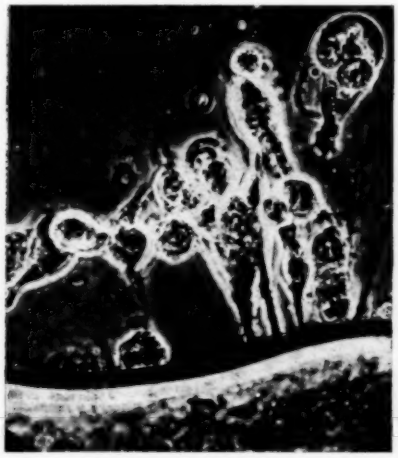

FIG. 2.—Appearance by phase contrast of cells of same tumour one hour after thawing. Cells lie at edge of an air bell (B), where a copious oxygen supply has induced rapid differentiation.

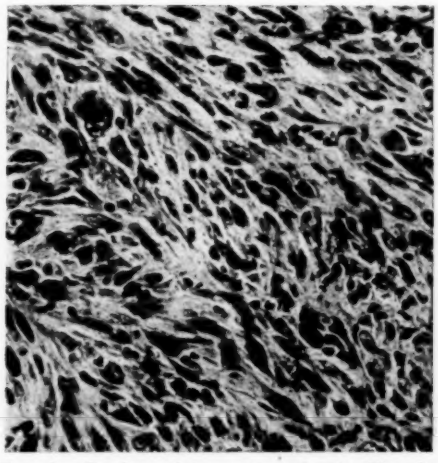

FIG. 3.—Section of tumour shown in Fig. A (Text). Tumour is a cellular spindle-cell sarcoma. (×280.)

H. B. FELL, E. MELLANBY, AND S. R. PELC: EXCESS VITAMIN A ON CHICK ECTODERM

FIG. 1*a*.—Control culture; 11 days in normal medium. Unstained section, phase contrast. Note cyst of squamous, keratinizing epithelium.

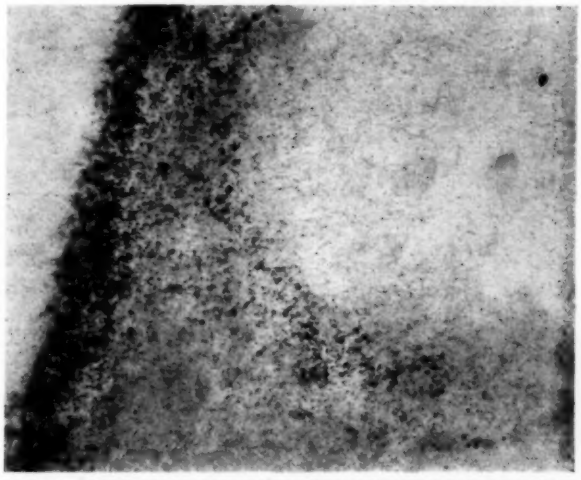

FIG. 1*b*.—Same section as Fig. 1*a* by ordinary lighting to show overlying autoradiograph. The blackening of the autoradiograph, due to $^{35}SO_4$, is considerable over the connective tissue but very scanty over the squamous epithelium.

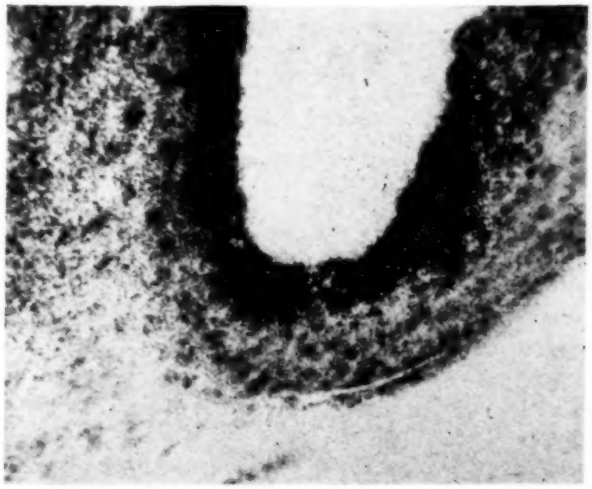

FIG. 2*a*.—+A culture; 11 days in medium containing 1,500 i.u. vitamin A per 100 ml. Unstained section, phase contrast. Note cyst of mucous epithelium.

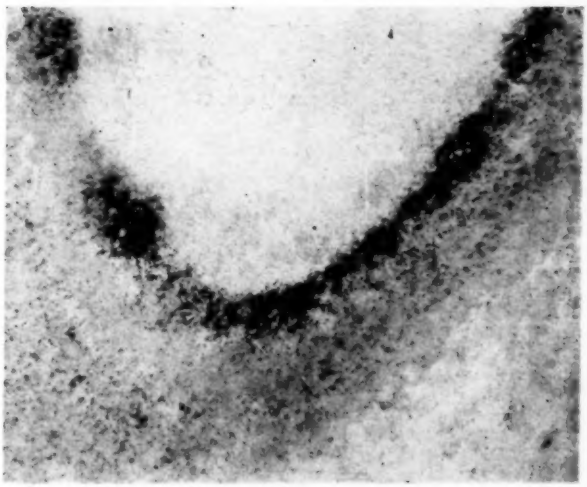

FIG. 2*b*.—Same section as Fig. 2*a* by ordinary lighting to show overlying autoradiograph. Note intense blackening over mucus-secreting epithelium due to $^{35}SO_4$.

P. J. N. COX AND R. J. P. PUGH: CHRONIC GALACTOSAEMIA

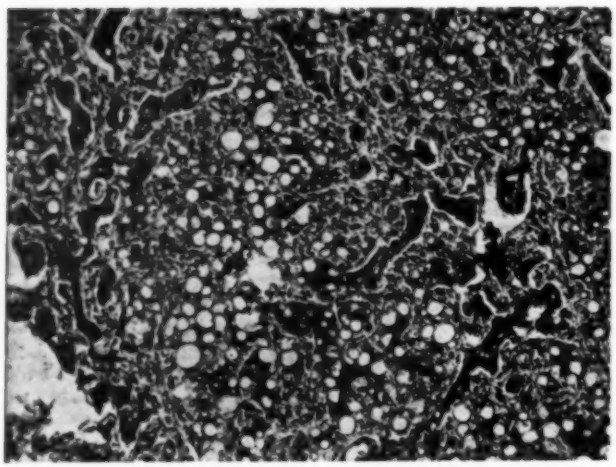

FIG. 1.—Case 4. Liver at necropsy. Fatty change, necrosis, and disorganization of parenchyma.

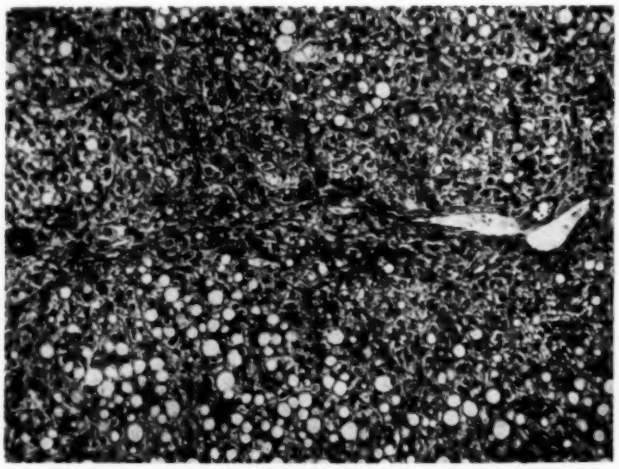

FIG. 2.—Case 5. Liver at necropsy. Gross fatty infiltration but less necrosis and disorganization than in Case 4.

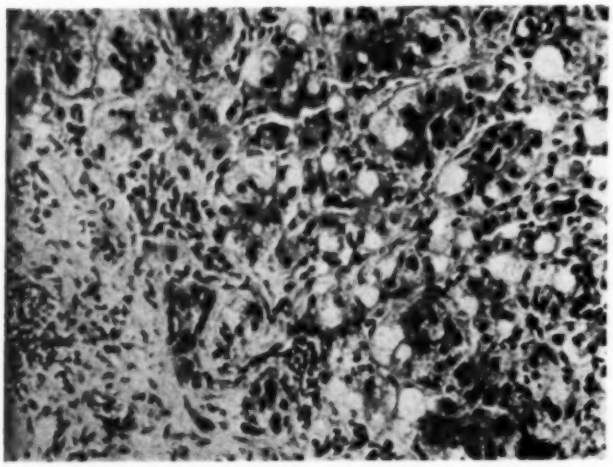

FIG. 3.—Case 6. Aged 3 weeks. Liver biopsy. Fatty change, necrosis, and early fibrosis.

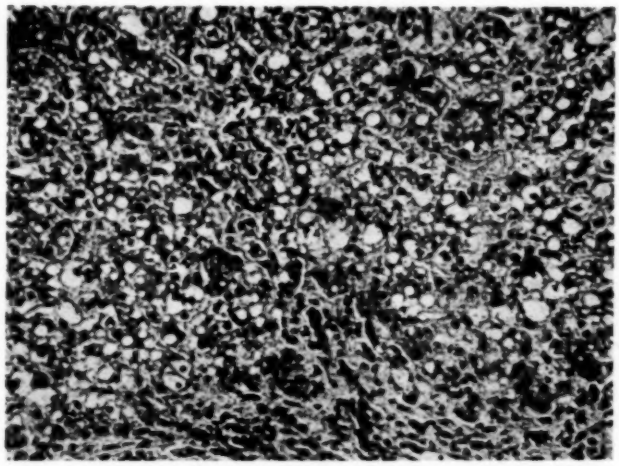

FIG. 4.—Case 6. Aged 11 weeks. Liver at necropsy. Fatty infiltration persists, but necrosis and fibrosis are less obvious.

D. J. ELLISON AND O. C. LLOYD: THROMBOTIC THROMBOCYTOPENIC PURPURA

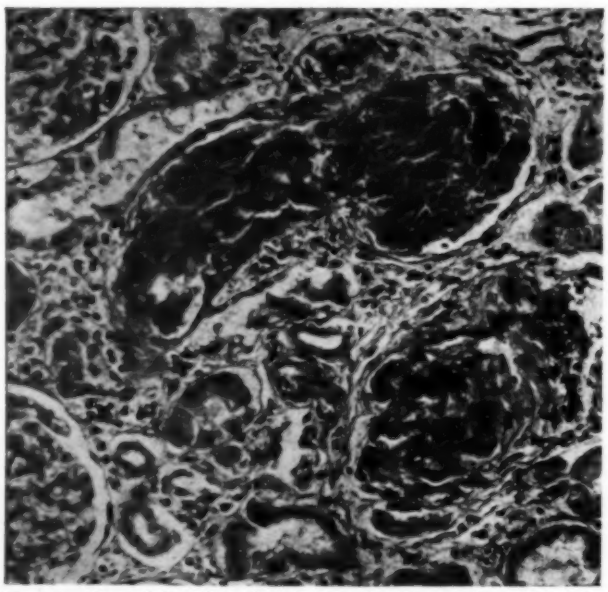

FIG. 1.—Organizing thrombus in two larger vessels, apparently venules. (Stained blue trichrome. ×150.)

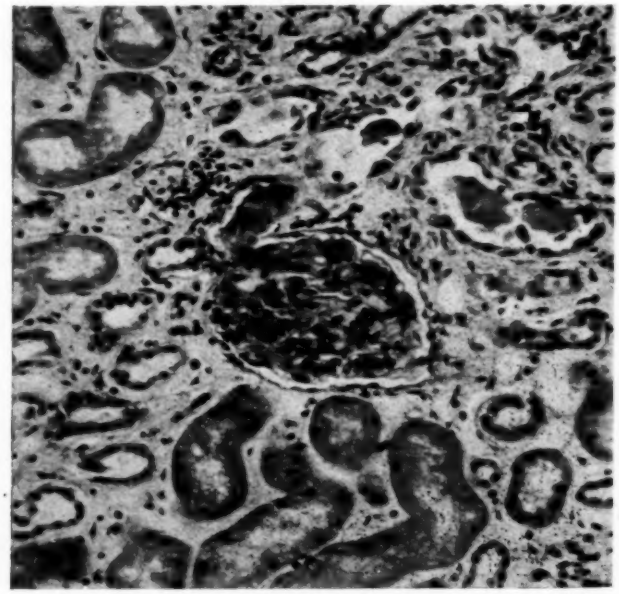

FIG. 2.—A glomerulus with thrombosis of one of its arterioles and some of its capillaries. Some of the neighbouring tubules are atrophied and there is interstitial fibrosis. (H. and E. ×150.)

INFLUENCE OF EXCESS VITAMIN A ON THE SULPHATE METABOLISM OF CHICK ECTODERM GROWN IN VITRO

BY

H. B. FELL, D.Sc., F.R.S.
Strangeways Research Laboratory, Cambridge

Sir EDWARD MELLANBY, G.B.E., K.C.B., F.R.S.
National Institute for Medical Research, London

AND

S. R. PELC, D.Phil.
Medical Research Council, Experimental Radiopathology Unit, Hammersmith Hospital, London

[WITH SPECIAL PLATE]

In previous experiments (Fell and Mellanby, 1953) it was shown that when the presumptive epidermis from 6–7-day chick embryos is grown in medium containing excess vitamin A (+A medium) it differentiates, not into the squamous, keratinizing epithelium of the skin as in normal medium but into a mucus-secreting, often ciliated, membrane resembling that of the nose. Recently an attempt has been made to investigate some of the biochemical changes which accompany this metaplasia, by studying the uptake of radioactive sulphur given in the form of the sulphate ($Na_2{}^{35}SO_4$) in ectoderm grown in normal and in +A medium.

Singher and Marinelli (1945) found that when labelled sulphate was injected into rats it was incorporated into chondroitin sulphate and related compounds; its incorporation into amino-acids was negligible in animal though considerable in plant tissues (Howard and Pelc, 1951). Dziewiatkowski *et al.* (1949) confirmed these findings in cartilage. Boström *et al.* (1952) demonstrated the uptake of sulphate in cartilage and also in mucous epithelium by means of autoradiographs, though the resolution was not sufficient to allow detailed investigation of the distribution and movement of the sulphate within the tissues. Using a different autoradiographic technique, Glücksmann and Pelc (1954) showed that in the tracheal cartilage sulphate is taken up by the cells and then diffuses into the matrix.

In unpublished experiments, Glücksmann *et al.* (1954) have found that sulphate is taken up readily by mucus-secreting cells, but only to a small extent by squamous, keratinizing epithelium. The object of the present investigation was to see whether cultures of ectoderm in normal and in +A medium, respectively, would show a similar difference in the uptake of sulphate corresponding with their histological development in the two media.

Present Investigation

The method was as follows. Fragments of ectoderm and underlying connective tissue were removed from the trunk and limbs of 7-day chick embryos and cultivated by the hanging-drop method (see Fell and Mellanby, 1953). Explants taken from one side of each chick were grown in normal medium (3 parts plasma and 1 part embryo extract) and those from the opposite side in the same medium to which had been added 1,500 I.U. of vitamin A alcohol per 100 ml. The tissue was transplanted every 48 hours. The results confirmed those previously described. In both the control and the +A series the ectoderm usually formed a closed cyst surrounded by connective tissue, but after seven to nine days' cultivation the epithelium in normal medium had assumed a squamous, keratinizing structure, while that in +A medium had formed a mucus-secreting membrane which sometimes was ciliated.

After seven days (two pairs of explants) or ten days (12 pairs) the coverslips bearing the cultures were detached from the hollow ground slides, and a drop of Tyrode's solution containing 200 μC. per ml. of $^{35}SO_4$ was deposited on each explant with a fine pipette. The drop was allowed to stand for about 30 seconds, after which it was sucked off, leaving only a thin layer of fluid over the tissue; the coverslip was replaced and re-sealed, and the preparation was returned to the incubator for about twenty-four hours. The cultures were then fixed for fifteen minutes in acetic alcohol, followed by thirty minutes in formol-saline; they were transferred from the fixative to 70% alcohol and the tissue was removed from the coverslip with a Bard–Parker knife. After being embedded in paraffin wax the cultures were serially sectioned. Autoradiographs were made by the stripping film technique (Doniach and Pelc, 1950).

There was a striking difference between the autoradiographs of the controls and those of the +A cultures. In the former (Plate, Figs. 1*a* and 1*b*), although the connective tissue and basement membrane were labelled, there was very little deposit over the epithelium and none over the keratin. On the other hand, in the +A explants (Figs. 2*a* and 2*b*) the connective tissue was labelled as before, but the basal cells of the epithelium had a higher content of sulphate than in the controls, and there was a dense autoradiograph over the inner secretory cells.

Summary

These results show that the sulphur metabolism of the presumptive epidermis of the chick converted into mucus-secreting epithelium *in vitro* by the presence of excess vitamin A in the culture medium is profoundly modified. In the controls, little sulphate is taken up by the squamous epithelium, which thus behaves like normal epidermis *in vivo*, whereas in the +A explants the utilization of sulphate is comparable to that of a normal mucous membrane in the body.

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The Report of the Director of Water Pollution Research (*Water Pollution Research 1953*, H.M.S.O., price 2s. 6d. net) contains an account of an investigation, requested by the Ministry of Housing and Local Government, to ascertain the extent to which radioactive isotopes in water would be removed when the water is treated at waterworks. Radioactive isotopes might contaminate the water supply as a result of enemy action or of discharge of effluents from industry, hospitals, or research establishments. Most of the work was done with radio-strontium, since this, according to the Report, is one of the most dangerous of the possible contaminants. Treatment with coagulants, at any rate in the concentrations normally used in waterworks, was ineffective, not removing more than 5% of the initial activity. Slow sand filters proved efficient at first, removing nearly all the activity, but with continued use they let through an increasing amount of radioactive material until by the fourteenth day their protective effect was negligible. However, softening of the water was much more hopeful. When calcium hydroxide and calcium carbonate were used, up to 75% of the activity was removed; lime, when the water was completely softened, removed 80%; and base-exchange softeners removed all but about 3%.

THROMBOTIC THROMBOCYTOPENIC PURPURA

REPORT OF A CASE

BY

D. J. ELLISON, M.B., M.R.C.P.Ed.

Late Senior Medical Registrar, Royal United Hospital, Bath

With Histological Examination by

O. C. LLOYD, M.D.

Lecturer in Pathology, University of Bristol

[WITH SPECIAL PLATE]

In 1924 Moschcowitz reported the case of a patient who died following a brief illness characterized by fever, haemolytic anaemia, a bleeding tendency, and terminal neurological signs. Histological examination revealed widespread hyaline thromboses in the capillaries and terminal arterioles. Baehr *et al.* (1936) described further cases and suggested that the thrombi were composed of masses of agglutinated platelets. The ensuing platelet deficiency was held responsible for the haemorrhagic tendency. This theory remains unproved, but no convincing alternative has been proposed. Thrombotic thrombocytopenic purpura is the most widely accepted name for the condition, and originates from Baehr's concept. Changes in the walls of the vessels underlying the thromboses are presumed to predispose to their formation (Gore and Friedman, 1948). Symmers (1952) has added an extensive review to the limited British literature on the subject. His two cases brought the published total to 38, the majority of them American. Not all have been well substantiated. Since then further cases have been described by Gendel *et al.* (1952), Barondess (1952), Cooper *et al.* (1952), and Blackman *et al.* (1952).

The following case, which is typical clinically, is reported because of the special histological features.

Case Report

The patient, a hospital matron aged 46, had an allergic rash in 1947. Thereafter she remained perfectly well until the onset at the end of December, 1951, of tiredness, loss of appetite, frontal headache, and continuous uterine bleeding. On January 12, 1952, she noticed that she was jaundiced, with dark urine and normally coloured stools. She was nauseated and vomited frequently. She denied exposure to drugs or to cases of hepatitis.

On admission to hospital on January 17 she was pale and jaundiced. Her temperature was 98° F. (36.7° C.), pulse 110, and respirations 16. There were scattered petechial haemorrhages in the skin of the upper part of the trunk and both arms, and in both conjunctival sacs. The fundi were clear. Hiss's test was negative. The liver, spleen, and lymph nodes were not enlarged. The apex beat was not displaced. A harsh localized systolic murmur was heard at the apex. The blood pressure was 160/100. The lungs and nervous system appeared normal.

Investigations.—The serial blood counts, E.S.R.s, absolute indices, and results of the flocculation tests are given in the accompanying Table. Bleeding time, 10 minutes; clotting time (capillary method), 6 minutes; clot retraction was deficient; prothrombin content, 100%; red-cell fragility, normal; direct Coombs test, negative; blood culture, sterile; agglutination reactions, negative; cold agglutinins, 1 in 4. Sternal marrow, reactive normoblastic hyperplasia. Urine: bile present; urobilin not present in excess; albumin, 0.1 g. per litre. Microscopically there were red cells and epithelial casts. Culture was sterile.

On the evening of January 17 her temperature was 100° F. (37.8° C.) and she complained of nausea and abdominal discomfort. Thereafter she ran an irregular pyrexia up to 105° F. (40.6° C.). Treatment was by repeated transfusions of whole blood. After each transfusion she appeared to be better for about twenty-four hours. Subsequently abdominal pain, nausea, vomiting, and headache recurred, fresh crops of petechiae appeared, and there was transient increase in the depth of jaundice. Apart from these fluctuations the jaundice steadily diminished, but it did not entirely disappear.

On January 22 she complained of numbness and weakness, affecting the lower half of the face and left arm. She showed a left facial weakness of upper motor neurone type with flaccidity, loss of power, and reduced tendon jerks in the left arm. The legs were normal, and both plantar responses were flexor. Re-examination on the following morning showed that these signs had entirely disappeared. Similar brief transient episodes involving the left face and arm occurred on February 4, 5, and 18; in the second and third of these her speech was slurred.

Thereafter she became increasingly weak, breathless, and confused. Altered blood appeared in the vomitus. A left hemiplegia developed on February 26, which did not fluctuate. She became comatose and died on February 28.

Permission for post-mortem examination was restricted to the abdominal organs. The body was that of a well-nourished middle-aged female, who was jaundiced and anaemic. Crops of purpura were present in the skin but not in the peritoneum. Macroscopically the abdominal organs appeared normal.

Histological Examination and Comment (Dr. Lloyd)

Evidence of haemolytic process was to be found in the spleen, which was congested and had large quantities of haemosiderin in the histiocytes of the pulp. Oddly enough a similar iron reaction was only very slight in the bone marrow. This marrow showed unusually active haematopoiesis, due to the haemolytic anaemia, and groups of haemocytoblasts also occurred in the hepatic sinusoids.

The principal thrombotic changes to be found in the smaller vessels were seen in the cortex of the kidney. Most of the vessels with thrombosis were venules (Plate, Fig. 1),

Haematological Data Other Than as Stated in Text

	Haemoglobin %	R.B.C. × 10^6 per c.mm.	Colour Index	Reticulocytes %	Mean Corpuscular Diameter	Packed Cell Volume	W.B.C. per c.mm.	Neutrophils %	Eosinophils %	Lymphocytes %	Monocytes %	Platelets per c.mm.	E.S.R.	Direct van den Bergh Reaction	Serum Bilirubin (Mg./100 ml.)	Colloidal Gold Test	Thymol Turbidity (units)
18/1/52 ..	50	2·9	0·9		7·2	24	6,300	68	3	25	4	40,000	40	Immediate +	7·5		
24/1/52 ..	71	3·95	0·9		7·2		7,000	73	2	15	10	70,000					
30/1/52 ..	44	3·1	0·7			20	7,700	71	1	10	18	60,000	68	Delayed +	1·25	++	2
6/2/53 ..	60	3·45	0·8	12·2		28	8,000	68	2	21	9	50,000	65	Delayed +	1·5		
14/2/52 ..	50	2·34	1·1	17·2		20	7,700	75	4	19	2	100,000	67	Delayed +	0·8	++++	8
20/2/52 ..	55																

No nucleated red cells or abnormal white cells were ever noted in the peripheral blood. Blood transfusions, each of 2 pints (1,140 ml.), were given on the following dates: 22/1/52, 31/1/52, 4/2/52, 9/2/52, 19/2/52, 21/2/52.

between 35 and 140 μ in diameter, but a few thrombi were seen in interlobular arterioles. The glomerular arterioles were rarely affected, but a few were found in which the thrombus extended into the glomerular hilum; it was not possible to say whether it was the afferent or efferent arteriole that was affected. In consequence of this relative immunity of arterioles the glomeruli were nearly all normal.

A remarkable degree of atrophy was present, however, in the tubules, with ischaemic fibrosis (Fig. 2). As the ischaemia was due to venous rather than to arterial obstruction, the pattern was entirely different from that seen in arteriosclerosis, and the ischaemic areas were scattered irregularly over the cortex.

Most of the thrombi showed signs of organization, and invasion by spindle cells, with formation of reticulin fibrils in the more recent, while the older showed collagenous scarring. Similar thrombi were to be seen in the arterioles and venules of the hepatic portal systems.

These microscopical findings are fairly typical of this disease. The two unusual features in this case are the thrombosis of venules rather than arterioles and the ischaemic fibrosis of the renal cortex. Symmers (1952) says that it is exceptional to find thrombi in venules, and that some authors claim that the supposed venules are dilated arterioles which have been misidentified. That cannot be so in the present case, as only a few of the thrombosed vessels are so far dilated as to make their identity doubtful. The relative paucity of ischaemic lesions is usually explained by the incomplete occlusion of many affected vessels. In this case, also, many vessels only seem to have been partially occluded by thrombus, but the ischaemic fibrosis is obvious. The haphazard distribution of the ischaemic areas is additional evidence that it is not mainly arterioles that have been obstructed.

Discussion

The correct diagnosis was not made during life, owing to lack of knowledge of the syndrome. There can be little difficulty otherwise in recognizing the fully developed case, with its four cardinal clinical features of haemolytic anaemia, thrombocytopenic purpura, fever, and terminal neurological signs.

In discussing the differential diagnosis, Symmers (1952) has stressed that thrombotic purpura must be considered wherever haemolytic anaemia and thrombocytopenic purpura are associated. Only thus can the diagnosis be made before the appearance of the essentially terminal neurological signs. Biopsy has an obvious place in diagnosis and, although the haemorrhagic tendency must limit the procedures undertaken, successes have been recorded with both skin and muscle specimens. Cooper *et al.* (1952) demonstrated the typical lesions in paraffin sections of aspirated bone marrow in both of their cases, but this is contrary to all previous experience.

In the above case the haemolytic origin of the jaundice was overlooked in the early stages. Its depth, the presence of bile in the urine and the absence of urobilin, and the positive flocculation tests suggested some form of hepatitis. Hirsch and Dameshek (1951) have stressed the frequency with which virus infections precede the onset of the acute form of thrombocytopenic purpura, and it was thought conceivable that a virus hepatitis could behave in this way. Furthermore, neurological signs are a recognized occurrence in liver failure (Walshe, 1951).

The only apparent therapeutic success is that of Meacham *et al.* (1951). In their case splenectomy was performed after an unusually early diagnosis, and was followed by a remission of three years' duration. No other patient has survived for more than ten months. Splenectomy has conspicuously failed in other cases, and the same applies to A.C.T.H., cortisone, various antibiotics, and repeated blood transfusions. Mepacrine has so far not been employed in the treatment of thrombotic thrombocytopenic purpura, but a trial of its effect seems justifiable, on empirical grounds, in view of the possible relationship between this disease and disseminated lupus erythematosus (Editorial, 1952; Symmers, 1952; Barondess, 1952). Page (1951) has reported the value of mepacrine in the treatment of some cases of the latter disease.

Summary

A case of thrombotic thrombocytopenic purpura is reported.

The characteristic thrombotic lesions were found in the renal cortex and hepatic portal systems.

The principal vessels affected were the venules. This is in contrast to previous reports, in which the changes have been found only in capillaries and terminal arterioles, and their occurrence in venules disputed.

Ischaemic fibrosis of the renal cortex was more evident than is usual.

I wish to thank Professor C. Bruce Perry for suggesting that this case should be reported, and Dr. D. W. Pugh for permission to publish and for criticism and advice.

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GALACTOSAEMIA

BY

P. J. N. COX, B.M., M.R.C.P., D.C.H.

Medical Registrar, the Hospital for Sick Children, Great Ormond Street, London

AND

R. J. P. PUGH, M.B., M.R.C.P., D.C.H.

Lecturer, Department of Child Health, University of Leeds

[WITH SPECIAL PLATE]

Children with galactosaemia are unable from birth to metabolize galactose normally. Galactose, derived from lactose in milk, accumulates in the blood and gives rise to enlargement of the liver, often jaundice, and commonly death in early infancy. The survivors develop cataracts, and are mentally deficient. Although this is a rare condition it is important that those who care for newborn babies should be familiar with it; with early treatment life can be saved, and a normal child may result. Diagnosis is thus more urgent than in most congenital metabolic anomalies.

The first clear account of this condition was published by Goppert (1917), although the case described by Von Reuss (1908) may also have been an example. Mason and Turner (1935) published the first American case report, and 12 others have since appeared, including papers by Townsend *et al.* (1951) and Donnell and Lann (1951) which incorporated reviews of the literature. Görter (1951) and De Haas (1951) have given brief accounts of three affected Dutch families. The first report from Great Britain is that of Bray *et al.* (1952).

Twenty-five proved cases have been found in the literature up to the end of 1952, and there are others in which the diagnosis is very likely. The object of this paper is to report a further six cases from three affected families, to describe the clinical picture, and to discuss the practical aspects of diagnosis and management of the condition.

Family I

The parents were unrelated; both were Rh-positive. The maternal Wassermann reaction and Kahn test were negative. The galactose-tolerance of the parents and surviving healthy child was normal.

Pregnancies:—Miscarriage. 1942: boy (Case 1); died aged 2 months. 1944: boy, normal child. 1946: girl (Case 2); died aged 39 days. 1949: boy (Case 3); surviving treated case. 1951: miscarriage.

Case 1

The patient, a male child, was born in 1942 following a normal pregnancy; birth weight 7 lb. 14 oz. (3.6 kg.). He was breast-fed. At the age of 2 months he was admitted to the Hospital for Sick Children with the history that from the beginning he had fed reluctantly, vomited frequently, and failed to gain weight; for three days his abdomen had been swollen and he had been lethargic and ill.

Examination revealed a pallid drowsy baby with generalized oedema, slight jaundice, and a distended abdomen with prominent superficial veins. The liver was palpable two fingerbreadths below the costal margin. The urine contained albumin ++, sugar ++++, no acetone, and no R.B.C., W.B.C., or casts. No further study of the urinary sugar was made. The child died early the next day following a series of fits.

Necropsy showed diffuse hepatic fibrosis, but no changes of importance in other organs; sections are no longer available.

Case 2

The patient, a female child, was born in 1946 following a normal pregnancy; birth weight 8 lb. 14 oz. (4 kg.). Her blood group was O Rh-positive (age 11 days). Direct and indirect Coombs tests were negative. She was admitted at the age of 8 days with the history that she had become jaundiced on the fourth day, and was losing weight.

On admission she was jaundiced and weighed 7 lb. 8 oz. (3.4 kg.); the liver was enlarged, the spleen was not. The right ear-drum was inflamed and the umbilicus was moist. The stools were normal in colour. The urine contained albumin 55 mg. per 100 ml., sugar +++, and a deposit of amorphous debris, with an occasional R.B.C., W.B.C., and epithelial cell.

Signs of sepsis disappeared following treatment with penicillin, but she failed to thrive, and the jaundice, after a temporary improvement, deepened. The alkaline serum phosphatase was 85 units, and the Takata–Ara test was negative (age 30 days). On the thirty-sixth day she developed diarrhoea and vomiting, and later vomited blood; the fontanelle was bulging and lumbar puncture yielded hazy xanthochromic fluid containing protein, 55 mg. per 100 ml.; sugar, 137 mg. per 100 ml.; chlorides, 710 mg. per 100 ml.; R.B.C., 2,405; W.B.C., 11. She died on the thirty-ninth day.

Necropsy.—The brain showed haemorrhage into the lateral ventricles and over the occipital lobes. The liver weighed 210 g. and was firm, with a finely granular surface. Histologically, there was gross disorganization of the liver pattern, with necrosis and fatty change of the liver cells, together with well-established mainly perilobular fibrosis. The pancreas showed marked islet-cell hyperplasia.

Case 3

The patient, a male child, was born on January 17, 1949; birth weight 8 lb. 3 oz (3.7 kg.). Initially he was breast-fed, and, like Cases 1 and 2, sucked poorly and failed to gain weight. Jaundice appeared on the seventh day and deepened gradually until his admission at the age of 2 weeks. He then weighed 7 lb. 1¼ oz. (3.2 kg.); the abdomen was not distended, but showed dilated superficial veins; the liver was felt two fingerbreadths below the costal margin; and the spleen was not palpable. The stools were normal. The urine contained albumin 140 mg. per 100 ml. and a deposit of amorphous debris with a few R.B.C.s. The direct Coombs test was negative (age 2 weeks). The jaundice faded during the following fortnight but he did not thrive. Owing to difficulty in feeding, he was changed at 1 month from the breast to a half-cream dried milk; he promptly gained 1 lb. (450 g.) in the course of five days. As the mother's milk supply was good, this sudden improvement may well have been due to the lower lactose content of the dried milk. His weight then remained stationary in spite of several changes of feed.

During the following year feeding difficulty persisted; he had bouts of vomiting, and gained weight very slowly. When he was about 1 year he had several slight fits, and at this time he was first noticed to have a squint. The liver remained enlarged to about 5 cm. below the costal margin, and the serum alkaline phosphatase was persistently raised (50–60 K.A. units); other liver function tests were normal. A liver biopsy (Mr. Denis Browne) at the age of 16 months showed a slight to moderate degree of perilobular fibrosis and fatty infiltration. Albuminuria continued, and the urine sometimes contained a few W.B.C.s and granular casts: the blood urea was slightly raised (55 mg. per 100 ml.).

At the age of 18 months the urine was found consistently to reduce Benedict's solution to red, and bilateral cataracts were noted. The suspicion that the urinary sugar might be galactose was confirmed by paper chromatography (Dr. Woolf); this showed a galactose content of about 1% in a morning specimen. Blood sugars were as follows:—fasting (12 hours): glucose 65 mg., galactose 33 mg., total 98 mg. per 100 ml. One hour after 8-oz. (230-ml.) milk feed: glucose 84 mg., galactose 41 mg., total 125 mg. per 100 ml. C.S.F.: glucose 103 mg., galactose 49 mg., total 152 mg. per 100 ml. A galactose-tolerance test showed a prolonged rise in blood galactose and moderate depression of blood glucose. About half the test dose was excreted in the urine (Fig. A).

The patient's developmental age at this point (age 18 months) was thought to be less than 6 months. There was gross retardation of growth, and the liver was still enlarged 5 cm. below the costal margin.

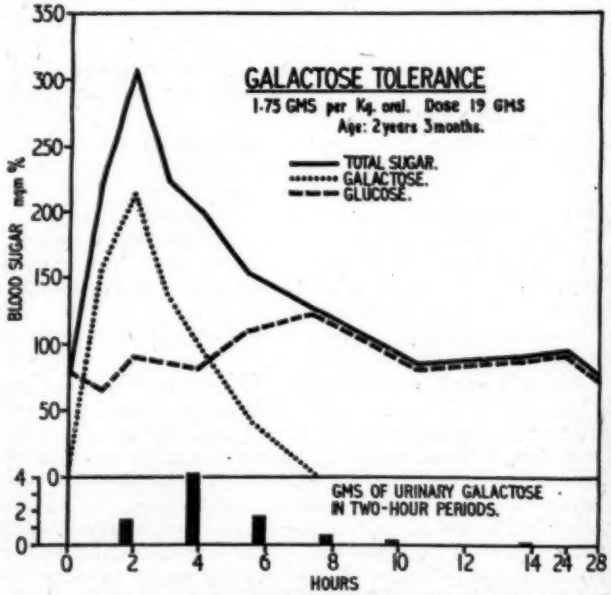

FIG. A.—Case 3. Galactose-tolerance test, showing blood total sugar, galactose, and glucose.

On August 25, 1950, he was started on a "lactose-free" diet (see discussion below). Sugar disappeared from the urine at once, and his albuminuria also diminished rapidly. Within a few days there was a striking improvement in his general condition: he became more alert and responsive and lost his previous anxious appearance. He did not gain weight during the first fortnight, but in the following six weeks he gained 4 lb. (1.8 kg.).

During the next year he made rapid progress in intelligence and physical development. Fig. B, his weight chart from birth, illustrates the striking effect of treatment and shows that between the ages of 18 months and 2½ years his weight was doubled; although remaining slightly below normal weight and height he has continued to gain steadily. A gradual decrease in the size of his liver was noted within a few weeks, and six months after the beginning of treatment this appeared normal, the edge being just palpable at the level of the costal margin. At the age of 2 years and 3 months his developmental age was regarded as about 9–12 months, and at 3 years and 4 months it was 15–18 months on the Gesell scale; at 4 years and 4 months his mental age (Merrill–Palmer scale) was 2 years and 5 months. At the age of 2 years and 3 months intermittent haematuria was noticed. This proved to be due to small renal calculi, lying probably in the minor calices of each kidney. The appearance did not suggest nephrocalcinosis. The calculi have not increased in size, and there is no impairment of renal function.

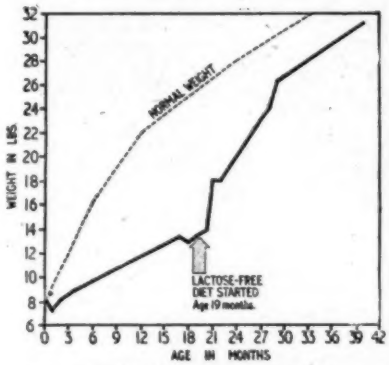

FIG. B.—Case 3. Weight chart, showing the effect of treatment.

After eight months on the lactose-free diet there was no change in the appearance of the cataracts, and in May, 1951, Mr. Doggart carried out discission of both lenses. The operation has since been repeated and the ocular media are clear, the child's sight with glasses being moderately satisfactory.

Family II

The parents were unrelated. The mother was O Rh-positive, Wassermann reaction negative; the father O Rh-negative.

Pregnancies:—1942: girl, normal child. 1946: girl (Case 4); died aged 27 days. 1951: girl (Case 5); died aged 8 weeks.

Case 4

The patient, a female child, was born in hospital following a normal pregnancy; birth weight 7 lb. 13 oz. (3.5 kg.). She was noted to be unduly sleepy by the fifth day of life, and by the sixth day was reluctant to feed and vomited frequently. She was subject to bouts of crying and head retraction. The abdomen became increasingly distended, and by the ninth day the liver edge had descended to the level of the umbilicus. Mild jaundice was then evident, the urine was bile-stained, and the stools were loose but well coloured.

Artificial feeding was first introduced on the eighth day, but breast milk was not entirely discontinued until the twelfth day of life, when also the appetite improved and vomiting ceased (cf. Case 3). Her weight gradually increased during the third week of life, but fell in the fourth week until death on the twenty-eighth day. The liver remained grossly enlarged, the edge extending to the level of the umbilicus, and there was also moderate ascites, with slight pitting oedema of the legs. A single observation of reducing substances, albumin, and bilirubin in the urine was recorded, but the nature of the sugar was not investigated.

Necropsy.—There was bile-stained ascites. The enlarged liver was olive green in colour and the histological picture was similar to that in Case 2. There was disorganization of the liver pattern by widespread necrosis, with gross fatty change in the surviving liver cells, and early fibrosis (Plate, Fig. 1).

Case 5

The patient, a female child, was born in 1951 in hospital; birth weight 7 lb. 2 oz. (3.2 kg.). Pregnancy had been complicated by hydramnios. At birth the infant was seen to have an extensive naevus on the outer aspect of the right thigh, which proved to be associated with absence of the internal saphenous vein on that side. By the end of the first week there had been a weight loss of 12 oz. (340 g.). She had become unduly drowsy, with vomiting and reluctance to feed, and there was mild dehydration. The liver margin descended progressively, reaching below the umbilicus by the twelfth day. The spleen was impalpable. Jaundice was absent throughout.

Urine examination on the twelfth day disclosed a reducing substance, maintained in consecutive specimens between 2 and 3%, and identified by paper chromatography as galactose. Fouchet's test for bilirubin was positive. No ketonuria was present. There was a slight general increase in amino-acid excretion, tyrosine, leucine, and proline being the most prominent.

Serial estimations of the blood-sugar levels before and after a 2½-oz. (70-ml.) breast-milk feed gave the following figures:

	Glucose	Galactose
Fasting	23 mg. per 100 ml.	130 mg. per 100 ml.
½ hour	58 " " " "	146 " " " "
1 "	46 " " " "	194 " " " "
1½ hours	58 " " " "	162 " " " "
2 "	46 " " " "	194 " " " "

The C.S.F. sugar was 111 mg. per 100 ml., of which 70 mg. was galactose and 41 mg. glucose.

From the fifteenth day a lactose-free feed was given. Galactose disappeared from the urine within 48 hours, and after a week clinical improvement was undeniable; appetite and vigour had both increased, vomiting had ceased, and she was no longer dehydrated. Most striking was the softening in the consistence of the liver, which diminished in size at first rapidly and then slowly, to reach half-way between the ribs and umbilicus four weeks after the exclusion of lactose. At the end of the first month of life the weight had mounted to 6 lb. 8 oz. (2.9 kg.), but from that time she did not thrive in spite of a generous calorie intake. Anorexia and occasional vomiting returned, and the stools were often undigested and loose. The liver again increased in size, and the infant died at the age of 8 weeks.

Necropsy.—The organs apart from the liver appeared essentially normal. The liver was enlarged (204 g.) and of a uniform yellow colour. Histological examination showed gross fatty infiltration, some necrosis, with only minimal disorganization of the liver pattern, and mild perilobular cirrhosis (Fig. 2).

Family III

Case 6

The patient, a male child, was born in hospital; birth weight 9 lb. 3 oz. (4.2 kg.). There was no parental consanguinity. The mother was group O Rh-positive and her blood Wassermann reaction was negative. There are two normal siblings aged 6 and 5 years.

The infant first caused concern on her fifth day of life by vomiting and passing loose green stools. These symptoms continued, with a resultant failure to gain weight. On the ninth day the conjunctivae appeared jaundiced, and bilirubin was detected in the urine. On the tenth day a brisk venous haemorrhage occurred from the umbilicus. The liver, which was readily palpable on the fifth day, had now enlarged half-way towards the umbilicus, and prominent veins had appeared over the upper abdomen. The spleen was not

felt at this time or subsequently. By the twelfth day the jaundice was deeper and there were signs of ascites. Spider naevi appeared on the inner aspects of the knees, but these did not persist beyond the third week.

Reducing substances were detected in the urine (2.5 g.%) on the fourteenth day. The sugar was identified as galactose by paper chromatography. The total blood sugar ranged from 240 to 151 mg. per 100 ml., about 70% of which was non-fermentable. There was considerable depression of blood glucose, to levels ranging from 17 to 54 mg. per 100 ml. Later (age 6 weeks) a typical galactose-tolerance curve was obtained. Feeding was exclusively by breast milk until transfer to a paediatric ward on the twenty-second day.

Laparotomy, with liver biopsy, was then undertaken immediately. The enlargement of the liver and the presence of ascites were confirmed. Histological examination showed considerable fatty change, with destruction of the lobular architecture and early fibrosis (Fig. 3).

A lactose-free feed was accepted readily from the beginning; vomiting and drowsiness ceased and the stools became normal. After two weeks the liver margin had ascended 1 in. (2.5 cm.), with resolution of the ascites and disappearance of the prominent abdominal veins, and the infant appeared altogether more vigorous. In spite of this initial encouragement there followed a gradual decline, with terminal new enlargement of the liver, anaemia, and convulsive movements (with normal blood calcium, CO_2 combining power, and blood sugar). Death occurred on March 18, 1953—that is, eight weeks after omitting lactose from the feeds.

Liver-function Studies.—Gross bilirubinuria, hyperbilirubinaemia, and a diminution of pigment in the stools were noted from the twelfth day. Within 12 days of lactose omission, bilirubin was no longer demonstrable in the urine, and did not reappear. The serum bilirubin fell more rapidly, to remain under 1 mg. per 100 ml. Bromsulphthalein excretion was initially grossly impaired (61% of dye still present after 45 minutes at 3 weeks of age), but this gradually approached normal, 16% and 11% remaining at 45 minutes, four weeks and six weeks respectively after lactose omission. Thus there was gradual improvement in liver function up to the time of the final relapse.

Amino-aciduria.—A gross excess of amino-acids was detected in the urine on the fourteenth day of life. This continued to the same degree (150–200 mg. per 100 ml.) until death, being unaffected by the withdrawal of lactose.

Necropsy.—The liver was fatty in appearance and weighed 180 g. Histologically, the liver lesion showed evidence of repair since the biopsy eight weeks before. There was still considerable fatty infiltration, but the lobular pattern was less disorganized and fibrosis had not extended (Fig. 4).

Clinical Picture

These three families illustrate well the clinical picture of the disease. Typically the infant, normal at birth, does not thrive from the first few days of life and is slow to regain its birth weight. There is great difficulty in feeding, with alternate lethargy and irritability, and often vomiting.

Wasting and mild dehydration are usual, but there may be oedema and ascites. Enlargement of the liver is the most constant sign; it appears during the first week of life, and may be accompanied by a palpable spleen. Jaundice is common (Cases 2, 3, 4, and 5); it was present in 14 out of 25 previously reported cases, being usually of short duration but occasionally lasting several months, as in Goppert's original case. Examination of the urine reveals a heavy reduction of Benedict's solution and usually albuminuria, often with a few cells and casts. The infant is at this stage very likely to die, either from infection or more directly from the effects of the disease. If this period is survived subsequent progress is slow and erratic; feeding difficulty continues and there is gross retardation of growth and mental development. Hepatic enlargement and glycosuria persist, and recurrent bouts of fever are common. Spontaneous bleeding may occur during the early weeks.

Cataract.—This was present in 15 out of 25 previously published cases; in those in which treatment was started before the age of 8 to 10 weeks changes in the lens were either absent or early and reversible, but all those above that age had definite cataracts at the time of diagnosis, with the exception of two infants aged 5 months. Similar cataracts are produced in young rats fed on a diet containing a high proportion of lactose or galactose (Mitchell and Dodge, 1935).

Cerebral Damage.—In addition to mental retardation there may be other evidence of cerebral dysfunction: our Case 3 exhibited fits, and later an unusual form of nystagmus which could not be explained entirely on the basis of ocular disease; one of the cases reported by Goldbloom and Brickman (1946) showed a transitory choreiform disturbance some years after starting treatment. Raised intracranial pressure due to cerebral oedema may be a feature in the newborn period (Case 1).

Amino-aciduria.—The urine was studied by paper chromatography in Cases 3, 5, and 6. While still on a milk diet all three showed a general increase in amino-acid excretion: in Cases 3 and 5 this was slight, but in Case 6 it was more considerable, amounting to 150–200 mg. per 100 ml. In Case 3 the amino-aciduria decreased rapidly when treatment was begun; in Cases 5 and 6, however, it persisted up to the time of death. This amino-aciduria probably reflects impairment of liver function, but it is not yet possible to define a consistent pattern and a renal origin has not been excluded.

Cerebrospinal Fluid.—Attention is drawn to the high C.S.F. sugars in Cases 2, 3, and 5. Figures of this magnitude are uncommon in infancy, and may provide a clue to the diagnosis in an unsuspected case.

Diagnosis

Galactosaemia must be diagnosed during the first few weeks of life if the infant is to have a chance of developing normally. Provided the urine of all sick infants is tested with Benedict's solution, cases in hospital at least will not be missed; it is important that this simple procedure, regarded as a matter of routine in older children, should not be neglected owing to practical difficulties. The condition should be suspected particularly in the presence of jaundice, hepatic enlargement, or a suggestive family history.

Consistent glycosuria is uncommon in infancy and should prompt a query regarding the nature of the reducing substance present. The most elegant and conclusive answer is given by paper chromatography, which was used to identify the sugar in our Cases 3, 5, and 6. When this technique is not available identification starts with the observation that the sugar is not fermented by yeast, thus excluding glucose and fructose; the osazone, mucic acid, and other chemical tests for galactose should then suffice for identification, although individually they are often inconclusive.

Galactose is sometimes found in the urine of other infants with liver disease, but it is then usually excreted only in small amounts, and often intermittently. Should the diagnosis be in doubt the persistently high blood galactose level, characteristic galactose-tolerance curve, and rapid response to treatment will differentiate the case of galactosaemia.

The condition should also be suspected in older children suffering from mental defect associated with cataract or liver disease (Fanconi, 1933; Bray *et al.*, 1952); if they are no longer on a milk diet galactosuria may be slight and intermittent, and a galactose-tolerance test should be done. There is no evidence so far that the metabolic error occurs in mild or incomplete forms, but should this be the case diagnosis might well be more difficult.

Treatment

The essential measure is the exclusion of lactose and galactose from the diet, and for infants a lactose-free milk must be contrived. We have used milk protein in the form of "casilan" mixed with coconut oil and arachis oil,

sucrose, and water. Butter contains lactose and is not suitable. Margarine can be used, but produces a less stable emulsion. In addition to vitamins it is necessary to add potassium, sodium, and iron salts, as casilan is deficient in these, but contains an adequate amount of calcium and phosphorus. Casilan contains about 1% of lactose, giving about 12 mg. of lactose (equivalent to 6 mg. of galactose) in each ounce of the feed referred to in our case reports as "lactose free." "Nutramigen" and soya milk, however, the lactose-free feeds recommended by previous authors, also include traces of galactose-containing sugars. A sample of "amigen," the amino-acid component of nutramigen, studied for us by Dr. Woolf, contained 0.7% of lactose, and a sample of soya milk contained stachyose and about 0.2% of raffinose, both of which contain galactose in the molecule, though it is not known whether galactose is liberated in the body.

Our three treated Cases (Nos. 3, 5, and 6) showed an almost immediate improvement in their general condition, with cessation of galactosuria and rapid decrease in size of the liver when the lactose-free diet was started. Case 3 continued to make good progress. Cases 5 and 6, however, both relapsed and died within a few weeks, with a terminal recurrence of gross liver enlargement.

This difference from published experience, which had led us to anticipate an uninterrupted recovery, may be due in part to selection. It is likely that cases have more often remained undiagnosed and unreported when the infants have died in the early weeks of life with severe liver damage than when they have survived to present a clinical problem over a long period, as in Case 3 and in many reports in the literature. Possibly treatment must be started earlier than two to three weeks after birth, which is the best that we have achieved, if survival is to be assured in every case.

On the other hand, the fatal outcome might be attributed to our inclusion of traces of lactose in the diet. Aminoaciduria is probably a sensitive indicator of impaired liver or kidney function in this disease; it is known that the addition of only 2 g. of lactose daily to the special diet may cause its return (Holzel *et al.*, 1952). In Case 3, an older child, amino-aciduria ceased when the casilan diet was started, while in Cases 5 and 6 it continued unabated until death. It may be that in a newborn infant the small quantity of lactose (about 200 mg. a day) included in our casilan diet was enough to prevent recovery, but we think this unlikely. It is possible, moreover, that traces of galactose are necessary in order to meet the body's requirements in the synthesis of essential compounds such as the cerebrosides and mucoids. Further information is needed on the effect of small quantities of galactose before these questions can be answered and a definite conclusion reached regarding the optimum diet for these infants.

As the child grows older it is probable that some milk-containing foods can be introduced into the diet without adverse effect (Townsend *et al.*, 1951), but it would be wise to prohibit the drinking of milk.

Prognosis

Without treatment survival is unlikely and mental defect is probably the rule. It might be expected that if lactose were removed from the diet soon after birth normal development would follow, but evidence for this is lacking. In only one recorded case has treatment been started in the first few days of life, and this child became mentally defective (Townsend *et al.*, 1951, Case T.F.). Nine other previously recorded cases have been followed for long periods (Norman and Fashena, 1943; Bruck and Rapoport, 1945; Mellinkoff *et al.*, 1945; Goldbloom and Brickman, 1946; Goldstein and Ennis, 1948; Townsend *et al.*, 1951): in these children treatment was delayed for periods ranging from seven weeks to two years, and all are mentally retarded or of borderline low intelligence except Bruck and Rapoport's patient, who was treated from the age of 2½ months, and was thought to be normal when 4 years old. In addition, there are several reports of apparently normal progress in infants still too young to be assessed with certainty.

It will be necessary to see the result of early diagnosis and treatment in many more cases before it can be decided whether the mental retardation is in fact due to cerebral damage occurring in the early weeks of life and resulting from the high concentration of galactose in the blood or to some other factor which is less amenable to treatment.

Genetics

The families reported by Goppert (1917), Fanconi (1933), Ellenburg and Peterson (1951), Görter (1951), and De Haas (1951) have been excluded from this discussion owing to lack of detailed information. The three families described above, together with the remaining published cases, give a total of 27 affected children in 17 families.

There is no known instance of cases occurring in more than one generation, and the few galactose-tolerance tests which have been performed on the parents of affected children have been normal. The familial incidence in this group, calculated from the ratio between affected siblings and total siblings after exclusion of the index cases, is 9 out of 31, or about 1 in 3.5. No instance of parental consanguinity has been reported, but unfortunately most authors have not mentioned this question. These limited figures, although naturally inconclusive, are consistent with a recessive mode of inheritance.

Morbid Anatomy

Patients with galactosaemia dying early in infancy usually show oedema of the brain, kidneys, and other viscera, but the only consistent change of importance is in the liver. The histology of the liver has been studied in biopsy or post-mortem material from five of our six cases, as described in the reports above. Our findings are similar to those in the seven previous cases in which the liver has been studied.

These twelve cases can be divided into two groups. In the first group of eight cases the age at the time of death or biopsy ranged from 8 days to 2 months (Bell *et al.*, 1950; Donnell and Lann, 1951; Edmonds *et al.*, 1952; and our Cases 2, 4, 5, and 6). These cases showed varying degrees of parenchymal necrosis and fatty change, with consequent disorganization of the liver pattern and abnormal arrangement of surviving cells, often in an alveolar type of grouping. The older members of the group also showed early hepatic fibrosis. The case described by Edmonds *et al.* (1952) is unusual in that the liver contained three isolated large nodules composed of glycogen-rich cells; the liver changes otherwise seem typical. The second group consists of four cases (Ellenburg and Peterson, 1951; Townsend *et al.*, 1951; Bray *et al.*, 1952; and our Case 3) examined at 4 years, 1 year, 1 year, and 18 months respectively. The livers of these older children showed only diffuse fibrosis and mild fatty infiltration, although the early clinical histories had been similar to those of the first group and, with the exception of the case of Townsend *et al.*, the diet contained lactose up to the time of examination.

It is evident that considerable liver damage occurs at an early age, probably during the first week of life; the severity of this damage may determine whether or not the child survives, but following this critical period repair occurs even though lactose is not removed from the diet. The liver lesion in older children is thus milder and perhaps non-progressive.

The reason for this contrast between the two age groups may lie in the immaturity of the liver in the younger infants, together with the higher concentration of galactose in the blood at this age. Comparison of the specimens from Cases 4 and 5 and of the two from Case 6 reveals differences which may be related to the effect of treatment rather than primarily to the differences according to age which are described above. Disorganization of the hepatic

parenchyma was more considerable in Case 4, who died untreated at 28 days (Plate, Fig. 1) than in Case 5, of the same family, who died at 8 weeks, six weeks after treatment was started (Fig. 2). Similarly in Case 6 considerable repair of the liver occurred in the course of eight weeks' treatment, as shown by comparison of the biopsy and necropsy specimens (Figs. 3 and 4). It is likely that the process of repair had initially progressed much further than the necropsy specimens suggest, since in both cases an unexplained relapse of liver enlargement and failure preceded death.

Biochemistry

The subject of normal galactose metabolism was last reviewed comprehensively by Deuel (1936). Galactose, together with glucose, is formed in the intestine by hydrolysis of the lactose in milk, and in normal milk-fed infants it is present in the blood only for short periods after feeds, although the concentration may then reach 20–30 mg. per 100 ml. (Hartmann *et al.*, 1953). Similarly, if a dose of 40 g. of galactose is given by mouth to a fasting adult (or 1.75 g. per kg. to a child) the concentration of galactose in the blood usually reaches 30–40 mg. per 100 ml. within an hour and falls to zero within two hours (Maclagan, 1940). Although the renal threshold for galactose is extremely low the total urinary excretion in this period does not normally exceed 2–3 g. (Shay and Fieman, 1937), because the galactose is removed rapidly from the blood by the liver (Bollman *et al.*, 1935). This observation forms the basis for the use of galactose tolerance as a test of liver function. Galactose is also utilized, although more slowly, by other tissues with the probable exception of those of the brain.

Direct evidence of the path of metabolism in the liver is lacking, but a speculative scheme can now be constructed (Kosterlitz, 1943; Caputto *et al.*, 1950; Garner and Grannis, 1951; Topper and Stetten, 1951). The first stage is phosphorylation by the enzyme galactokinase to form galactose-1-phosphate; the latter is converted to glucose-1-phosphate, this process involving an enzyme "phospho-galactoisomerase"; glucose-1-phosphate is then converted into glycogen.

In children with galactosaemia utilization of galactose is greatly impaired, possibly owing to the absence or inhibition of one of these enzymes. A galactose-tolerance test shows a high and prolonged rise in blood galactose with depression of blood glucose, and while the child is on normal milk feeds the blood galactose remains high throughout the day and galactose is excreted in the urine. The rapid relief obtained when lactose is omitted from the feeds suggests that these children's symptoms are due chiefly to the toxic effect of this high blood galactose concentration, although the depression of blood glucose which also occurs (as in Cases 3, 5, and 6) may play a part. Mason and Turner (1935) suggested that the depression of blood glucose results from overproduction of insulin in response to the high blood galactose, which itself is unaffected by the insulin produced. In this connexion it is interesting that the pancreas from Case 2 showed striking islet-cell hyperplasia; unfortunately we have no information about the blood sugar in this infant, and changes in the pancreas do not seem to be the rule; in Cases 5 and 6 the pancreas was normal, and in our other cases it was not examined.

Galactose is an essential cell constituent, in particular as a component of the cerebrosides of nervous tissue and of the mucoids, and possibly plays some part in the metabolism of fat (Richter, 1948). It is not known whether these and other ill-understood functions of galactose are also disordered in children with galactosaemia.

Summary

The possibility of galactosaemia should be considered in infants who fail to thrive from birth and develop enlargement of the liver, with or without jaundice.

A provisional diagnosis can usually be made by testing the urine with Benedict's solution.

Early treatment may save life and prevent the development of cataract and mental defect.

Six cases are reported; the histology of the liver was studied in five.

We are indebted to Professor W. S. Craig and Professor Alan Moncrieff for permission to report these cases, and to Dr. W. W. Payne, Dr. L. I. Woolf, and Mr. F. J. N. Powell for advice and for the biochemical estimations. Dr. Martin Bodian and Dr. W. G. Goldie examined the livers of these infants, and Dr. C. O. Carter helped in the diagnosis and in the discussion on genetics. Dr. Katharine Dodd, Professor Gladys Fashena, Dr. Alton Goldbloom, and Dr. Eugene Goldstein kindly provided information on the progress of cases previously reported elsewhere.

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CONGENITAL GALACTOSAEMIA

REPORT OF A CASE

BY

M. W. ARTHURTON, M.D., M.R.C.P., D.C.H.

Consultant Paediatrician, Dewsbury, Batley, and Mirfield Hospital Group; formerly Senior Registrar, Westminster Children's Hospital

AND

B. W. MEADE, M.D.

Senior Registrar and Pathological Tutor, Department of Chemical Pathology, Westminster Medical School

Since Von Reuss (1908) described this condition some 30 cases have been recorded, principally in America and Germany. Bray *et al.* (1952) have reviewed the literature in presenting three cases in Britain. We report this further case not only because of the comparative rarity of the condition but because of its association with some unusual biochemical findings. The importance of early recognition of the disease as a cause of failure to thrive in infants must be emphasized, for it is capable of cure, but if treatment be delayed blindness, mental defect, or death may ensue.

Case History

A male infant 4 weeks old was admitted under the care of Dr. I. M. Anderson on September 9, 1952, from a neighbouring maternity unit because of failure to thrive. His birth weight was 6 lb. 12 oz. (3.1 kg.), following a normal pregnancy and delivery. Jaundice of moderate severity, first noted on the third day of life, persisted for two weeks in association with pallor and hepatomegaly. From the fourth day a varying degree of lassitude and anorexia was observed and the weight gain was poor and erratic. The mother's lactation failed on the ninth day, so full-cream National dried milk was substituted.

Family History.—Parents and three sibs were well. In 1946 a premature baby weighing 4 lb. 4 oz. (1.9 kg.) died aged 3 weeks of undetermined cause, although the symptomatology resembled that of the present case. (Unfortunately no case notes are available.) There was no history of consanguineous marriages.

On examination his weight was 6 lb. 8 oz. (2.9 kg.). He was afebrile, pale, and wasted. The head circumference was 13½ in. (34 cm.). The liver and spleen were palpable 6 cm. and 1 cm. respectively below the costal margin. The urine contained a trace of albumin. No other abnormal clinical findings were noted on admission. The provisional diagnoses considered at this time were: (1) A chronic infection, possibly renal; but none could be detected, and microscopically the urine was normal. (2) Congenital syphilis. The negative serology in mother and infant and the absence of clinical evidence of the disease apart from hepatosplenomegaly were against this diagnosis. (3) Erythroblastosis foetalis with secondary cirrhosis of the liver. This possibility was supported by the initial haematological examination (Dr. K. Goldsmith), which showed: Hb, 79%; blood group A, Rh positive; direct Coombs test, weakly positive. The maternal blood was group O, Rh positive. Serum examination showed an anti-A titre 1/64; after suitable absorption immune anti-A titre 1/16. Haemolysin was present to a titre of 1/8. "These findings strongly suggested that the child was affected by an immune anti-A antibody developed by the mother, probably as a result of her pregnancy."

Examination of the urine with Benedict's solution, however, yielded an orange precipitate, but tests for ketone bodies were negative. A provisional diagnosis of galactosaemia was made, and this was confirmed biochemically. The relevant laboratory data were as follows:—*Blood* (three hours after feeding): fermentable sugar, 52 mg. per 100 ml.; non-fermentable sugar, 205 mg. per 100 ml.; serum sodium, 144 mEq/litre; serum potassium, 5.1 mEq/litre; plasma inorganic phosphate, 4 mg. per 100 ml.; alkali reserve, 15.5 mEq/litre; chlorides, 126 mEq/litre; total bilirubin, 1.4 mg. per 100 ml.; plasma amino-acid nitrogen, 5.2 mg. per 100 ml. Other liver-function tests, including alkaline phosphatase and turbidity tests, were within normal limits for a child of this age. *Urine:* albumin, 38 mg. per 100 ml.; *p*H, 8; yeast fermentation test, negative; mucic acid test, positive; total "non-fermentable" sugar, 1.62 g. per 100 ml.; paper chromatography (C. H. Bowden), reducing substance behaved as galactose; two-dimensional paper chromatography revealed alanine, glycine, and serine spots of normal intensity. The urine of both parents and all siblings failed to reduce Benedict's solution on two separate occasions.

Mr. Trevor Roper reported "striate opacity in both lenses."

On September 22 a daily formula was started of "casilan," 1 oz. (31 mg.), glucose, 2 oz. (62 mg.), arachis oil, ¾ oz. (21 ml.), made up to 24 oz. (680 ml.) with boiled water. This diet was supplemented with iron and vitamins, and in view of the laboratory evidence of acidosis 4 g. of sodium citrate was also given daily for seven days. The synthetic feed was well taken and tolerated, and within 24 hours of its institution the blood and urine chemistry returned to normal. After a week the child had gained 7 oz. (200 g.), the liver was felt only 4 cm. below the costal margin, and the lens opacities showed marked regression.

Further progress was unfortunately interrupted by the development of a severe gastro-enteritis of undetermined aetiology, necessitating intravenous therapy.

The lactose-free formula was recommenced on October 9, and was altered to contain casilan 20%, olive oil 18%, arrowroot starch 10%, dextri-maltose 48.5%, calcium gluconate 3.5%. In addition sodium chloride, 1 g., and potassium chloride, 1 g., were given each day. Subsequent progress was excellent until December 23, when the patient weighed 10 lb. 5 oz. (4.7 kg.). Thereafter there was a slow fall in weight, for which no cause could be discovered. The serum potassium level remained steady, however, at approximately 5.7 mEq/litre, and hence on January 10, 1953, the potassium supplement was discontinued. Instead of improving, the patient became more apathetic, and three weeks later the serum potassium had fallen to 1.9 mEq/litre. Daily supplements of 1 g. of potassium chloride were restarted with dramatically good results, but the weight gain, despite normal blood chemistry, was disappointing except when Darrow's solution was given orally in addition to the other supplements. On February 24 potassium citrate, 0.7 g. daily, was accordingly substituted for potassium chloride, and thereafter the weight gain was satisfactory. Oedema appeared on March 16, but was dispelled by the reduction of daily NaCl supplement to 0.75 g.

On April 1 mixed feeding was slowly introduced. In order to facilitate food preparation by the mother after the child's discharge from the hospital, the synthetic formula was replaced by "nutramigen" (a product containing dextri-maltose 42%, co-nutren 20%, corn oil 18%, arrowroot starch 10%, calcium gluconate 3.5%, other salts 3.2%), of which he received 16½ measures (each of 5-ml. capacity) daily in 22 oz. (625 ml.) of water with 3 dr. (12 g.) of added sugar. He was receiving, in addition, a full toddler diet with a daily supplement of 0.75 g. of sodium chloride. A galactose-tolerance test on April 16 gave a grossly abnormal result, as follows (dose 1.75 mg. per kg.): ½ hour 24 mg., 1 hour 72 mg., 1½ hours 80 mg. per 100 ml.

When the patient was discharged on June 11, at the age of 10 months, his condition was as follows: weight, 18 lb. 1 oz. (8.2 kg.); head circumference, 17¾ in. (45 cm.); crown–heel length, 28 in. (71 cm.); six teeth present; liver 2½ cm. below costal margin, smooth but firmer than normal; unable to sit up unaided; mental age estimated at approximately 5 months.

Mr. Trevor Roper reported persistence of the small opacity in the posterior pole of the left lens. The blood sugar, alkali reserve, plasma chlorides, serum sodium, and potassium were all within normal limits.

When he was seen after discharge from the hospital, at the age of 12 months, the findings were: weight, 20 lb. 10½ oz. (9.4 kg.); crown–heel length, 31 in. (79 cm.); head circumference, 18¾ in. (47.5 cm.); 10 teeth present; liver soft, smooth, and only just palpable; remained sitting when assisted into upright position; not yet crawling; sees and hears normally; mental age assessed at 8 months. Mr. Trevor Roper reported that the small central opacity in the left lens was still present, but that it would not affect the child's vision.

Discussion

Studies on galactose-fermenting yeasts have suggested that the probable metabolic route of galactose is:

(A) Galactose+adenosine triphosphate→galactose-1-phosphate
(B) Galactose-1-phosphate→glucose-1-phosphate.

As demonstrated by Trucco *et al.* (1948), reaction A is catalysed by the enzyme galactokinase, whilst B involves the enzyme phosphogalactoisomerase, which has been isolated from adapted strains of *Saccharomyces fragilis* by Garner and Grannis (1951), and the co-enzyme uridine-diphosphate glucose demonstrated by Caputto *et al.* (1950) not only in yeast preparations but also in rat kidney, brain, muscle, and to a less extent liver.

From the glucose-1-phosphate stage the metabolism is probably that of glucose. This proposed sequence of events

is supported by the observations of Topper and Stetten (1951), who fed D-galactose-1-C^{14} to rats and recovered glycogen from the liver which, on hydrolysis, yielded glucose having 90% of its isotope content in position 1. Thus inhibition or lack of any of the enzyme systems involved in reactions A or B would appear a possible lesion in these children. That disease may arise from such a lack of a specific enzyme system has been elegantly established by Cori and Cori (1952), who demonstrated lack of glucose-6-phosphatase activity in liver homogenates from certain cases of glycogen storage disease.

Alternatively the galactosaemia could arise as a result of hepatic damage, following immunization. The galactose-tolerance tests would offer no help in differentiating this secondary defect and the primary defect mentioned above. Bessis (1947) demonstrated profound histological changes in the liver in cases of fatal icterus gravis, but Gerrard (1952) could detect no significant residual hepatic damage in cases surviving Rh sensitization. Gorter (1951) reported galactosuria occurring in association with A–O blood group incompatibility, and in the mother of the present case an anti-A agglutinin was detected. However, Townsend *et al.* (1951), reviewing the relationship between galactosuria and Laennec's cirrhosis, concluded that the defect of galactose metabolism was primary and that the cirrhosis was secondary. This conclusion is supported by the normal liver-function tests in our case.

Bray *et al.* (1952) detected an excess aminoaciduria in two of their cases, but no observations were recorded on the blood amino-acid nitrogen. We were unable to detect this urinary abnormality on two separate occasions. Such an aminoaciduria might result either from liver damage or from renal tubular deficiency. It is noteworthy that the initial biochemical findings in our case resembled those of infantile renal acidosis. Latner and Burnard (1950) have ascribed this condition to failure of the proximal renal tubule to reabsorb bicarbonate ions.

It is conceivable that both these tubular lesions causing excess aminoaciduria and failure of bicarbonate resorption have arisen as toxic manifestations of the galactosaemia, but it must be admitted that we need to study many more such cases before any final conclusion can be reached, and that the association of the acidosis and galactosaemia may be fortuitous.

Summary

The clinical and pathological findings and response to treatment of a case of galactosaemia associated with hyperchloraemic renal acidosis and haemolytic disease of the newborn is described.

It is thought that galactosaemia arises as a congenital condition due to a specific lack of enzymes involved in the metabolism of galactose.

The possibility that the renal acidosis arose as a result of the toxic effect of galactose on the renal tubules is considered.

We are indebted to Dr. I. M. Anderson, whose case this was, and Professor N. F. Maclagan for their advice, help, and criticism in the preparation of this paper, and to Dr. K. Goldsmith for the haematological investigations.

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OPERATIVE CHOLANGIOGRAPHY

BY

E. S. R. HUGHES, M.S., F.R.C.S., F.R.A.C.S.
Assistant Surgeon, Royal Melbourne Hospital

AND

R. H. KERNUTT, M.S., F.R.A.C.S.
Surgical Registrar, Royal Melbourne Hospital

Surgeons are divided in their opinions concerning the value of radiology in the detection of stones in the common bile duct despite the unreliability of the usual surgical methods. Some have come to regard operative cholangiography as indispensable in the surgery of the biliary tract (Mallet-Guy *et al.*, 1947; Mirizzi, 1948; Hicken *et al.*, 1950; McNeill Love, 1952); others have criticized the investigation as being cumbersome, unnecessary (Maingot, 1952), and unsatisfactory because of a susceptibility to appreciable error in interpreting the films at the time of the operation (Waugh *et al.*, 1952).

The bile ducts can be visualized radiologically only after they have been filled by a direct injection of radio-opaque medium. Attempts have been made to do this before operation, but as yet there is no satisfactory standard method.*

Diagnostic Operative Cholangiogram.—The injection into the common bile duct is made after the abdomen is opened and just before the dissection on the biliary tract is begun. The film is developed at once; a stone will be visible as a filling defect.

Control Operative Cholangiogram.—When the common bile duct is opened it is customary after exploration to insert a tube into the duct for the purpose of external biliary drainage. Before the abdominal cavity is closed opaque medium can be injected down the tube into the duct and a further film taken. If an overlooked stone is disclosed the duct is re-explored.

Present Investigation

Operative cholangiography has been performed in a series of 50 patients subjected to operation on account of gall-stones. The investigation was conducted with a view to ascertaining the practicability or otherwise of operative cholangiography as a routine procedure; the value or otherwise of operative cholangiography in the diagnosis of stones in the common bile duct; the apparent advantages of control operative cholangiography over post-operative cholangiography; and the place of operative cholangiography in the recognition of disorders of the biliary tract coexisting with gall-stones.

Technique

Three ureteric catheters (sizes 4 F., 5 F., and 6 F.) and a 20-ml. syringe with blunt needles fitting the corresponding catheters are needed. The medium used is a 35% solution of diodone ("pyelosil 35"). A 50% solution ("pyelosil 50") has been employed in the more obese without ill effect. Diodone contains 49.8% by weight of iodine. It is comparatively free from tissue irritation.

The middle segment of the rubber mattress on the operating table is replaced by a flat tunnel constructed of three-ply wood. The tunnel is long enough to take an *x*-ray plate 11 by 14 in. (28 by 35.5 cm.) and to allow for some readjustment to bring it to lie under the biliary tract, and high enough to accommodate the cassette and Lysholm

*This paper was prepared just prior to experiments with intravenous cholangiography; results have been encouraging.

grid. Such a tunnel is not essential, but it facilitates the removal and replacement of the *x*-ray plate. The portable *x*-ray machine is wheeled to the left side of the table.

The operation proceeds in the usual way. The viscera are packed away, the fundus of the gall-bladder is held in artery forceps, and the cystic duct is defined and isolated. A length of fine silk is threaded around the cystic duct but not tied. A second ligature is tied around the

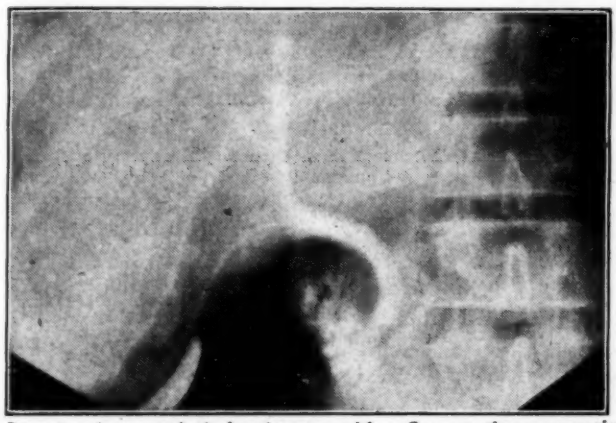

FIG. 1.—A normal cholangiogram with reflux up the pancreatic duct. Tributaries join within the liver to form the right and left hepatic ducts. The common hepatic duct and upper part of the common bile duct run medially, but then curve gently to the right to allow a more vertical course for the lower half of the common duct. Diodone has entered the duodenum.

cystic duct at its junction with the gall-bladder. A small cut is made in the cystic duct and a ureteric catheter of suitable diameter is inserted down into the lumen of the common bile duct for 4–5 cm.

The syringe containing 20 ml. of diodone is supplied with a needle that accurately fits the ureteric catheter, and 1–2 ml. is injected down the catheter to confirm that there will be no leakage of medium around it. All overlying instruments are removed; a pack is placed over the wound; the operating table is rotated 20 degrees to the right side; 10 ml. of diodone is injected as rapidly as possible, and at the conclusion of the injection the anaesthetist stops respiratory movements and the first film is taken (diagnostic operative cholangiogram).

Whilst the film is being developed the excision of the gall-bladder proceeds in a routine way, and often the surgeon has largely re-peritonized the gall-bladder fossa by the time the film is ready. If the film is unsatisfactory a further one can be taken at this stage, because the ureteric catheter has been left *in situ*. If the film is satisfactory and no stones are present, the ureteric catheter is removed and ligation of the cystic duct completed.

If the film shows or suggests the presence of a stone the common duct is explored. After this has been completed a tube is sutured snugly into the duct. An *x*-ray plate is reinserted and a second cholangiogram performed (control operative cholangiogram). The abdominal wound is not closed until this film has been developed, because if it should reveal a stone that has eluded the surgeon a further exploration is required.

Normal Operative Cholangiogram

The intrahepatic radicles are displayed, and, as tributaries join within the liver, the right and left hepatic ducts finally emerge, joining to form the common hepatic duct (Fig. 1). The common hepatic duct and the upper part of the common bile duct run medially, then curve gently to the right to allow the lower common bile duct to take a more vertical course, parallel to the spine, to end at the level of the second lumbar vertebra. The lower end of the common duct tapers abruptly into the intramural portion, which can often be followed into the duodenum. There may be reflux up the pancreatic duct for 3–4 cm. Some medium should be visible in the duodenum.

Abnormal Cholangiogram Due to Biliary Calculi

Calculi usually appear as filling defects in the common bile duct shadow and particularly at its lower end (Fig. 2). The duct above is often dilated. In some cases no dye enters the duodenum, presumably because the stone is within the intramural part. In some films rounded shadows of lesser density suggest the presence of stones in the intrahepatic radicles.

Results

Technical Aspects.—There were no deaths in this series of 50 cases, and the only complication which could be attributed to operative cholangiography was an acute dilatation of the stomach. There were five unsatisfactory films; in one case the diaphragm moved at the moment of the exposure, in another a pair of forceps concealed the outline of the lower end of the common bile duct, whilst in a third the film was incorrectly centred. In two other cases the lower end of the common bile duct was obscured by excessive dye in the duodenum.

Diagnostic Operative Cholangiography.—In 32 instances the cholangiogram was accepted as being within normal limits, and the common bile duct was not explored. In one of this "apparently normal" group biliary colic occurred on the second post-operative day; re-examination of the *x*-ray film revealed a small filling defect which had been overlooked in the operating theatre when the film was wet. In 12 cases stones were visualized as filling defects and were removed. In three no dye entered the duodenum, and from two of these stones were removed from the common bile duct. In three other patients the common bile duct was explored because it was thought that the wet

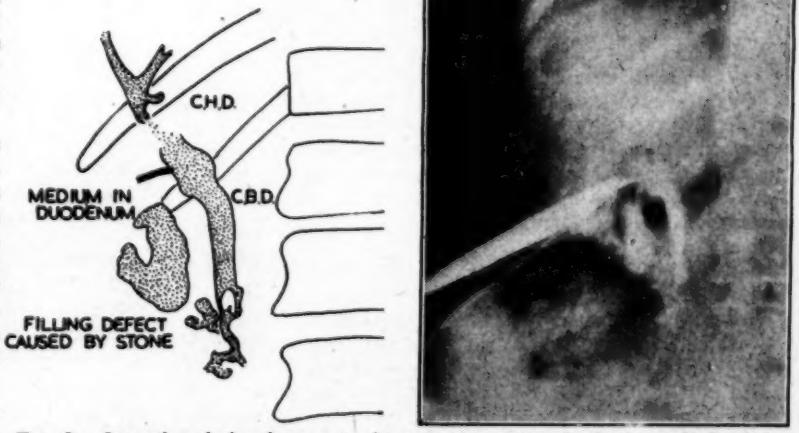

FIG. 2.—Operative cholangiogram to demonstrate a stone in the lower part of the common bile duct. Opaque medium has entered the duodenum. Note the normal narrow intramural portion of the common bile duct immediately below the stone.

films were abnormal, but no stones were found. In the whole series of 50 cases the duct was explored on 18 occasions, and stones were removed in 14.

Control Operative Cholangiography.—Control operative cholangiograms were performed on 10 of the 14 patients from whom stones were removed from the common bile duct; in one of these an overlooked stone was discovered and removed, and a second control operative cholangiogram showed normal ducts.

Detection of Other Conditions.—In one cholangiogram no medium entered the duodenum and no stone was found in the common bile duct on subsequent exploration; a

diagnosis of "hypertonic sphincter" would be permissible. Other than passing a fine sound into the duodenum no treatment was adopted, and the patient has since remained free of symptoms. No case in this series showed cholangiographic evidence of atonic sphincter. On two occasions on which there was considerable fibrosis around the junction of the cystic duct, common hepatic duct, and common bile duct an operative cholangiogram proved of assistance in displaying the anatomical arrangements of the ducts prior to their actual dissection. In this series of 50 cases a pancreatic reflux was observed in eight, but it appeared to be of no significance.

Discussion

Practicability of Routine Operative Cholangiography

This investigation has shown that the technical aspects of operative cholangiography need not be burdensome; the procedure prolongs the operating time, but has proved harmless to the patient—with the possible exception of one case of acute gastric dilatation. An early disappointment should not deter the surgeon from persevering. With attention to detail, satisfactory films can be obtained in a high proportion of cases with little inconvenience.

A ureteric catheter is better than a fine rubber catheter for conveying the dye—its rigidity facilitates negotiation of the valves of Heister (often a tedious procedure) and its centimetre ring graduation enables the surgeon to estimate at once the length of the catheter in the common bile duct. Needle puncture of the common bile duct is less reliable; if the gall-bladder has already been removed or if it proves impossible to gain entry through the cystic duct it may be necessary to use a needle, but even in these cases it is easier to push a ureteric catheter into the duct through a small puncture wound made by a needle; a catheter enables a second picture to be quickly taken if the first should prove unsatisfactory, and at the same time it allows the surgeon to keep his hands well away from *x*-radiations.

Respiratory movement must cease when the film is taken. For this reason controlled respiration anaesthesia is necessary, and, as the *x*-ray machine should be used in the absence of inflammatory gases, the anaesthetic of choice is nitrous oxide and oxygen, with endotracheal intubation and the use of a relaxant.

It is important to visualize clearly the terminal portion of the common bile duct. Interference by the lumbar vertebrae can be overcome by rotating the operating table. As the dye runs into the duodenum the folds of that viscus may overlap the terminal duct and conceal its true outline. This can be partly avoided by taking the first film immediately the injection is completed and before too much dye has entered the duodenum.

Place of Operative Cholangiography in the Diagnosis of Stones in the Common Bile Duct

The experience obtained in this series indicates that operative cholangiography can afford some assistance in diagnosing the presence of stones in the common bile duct, although it will probably only rarely disclose a stone the presence of which should not at least have been suspected by the surgeon. When the 14 positive cases of common bile duct stones were reviewed it was apparent that in 13 there were definite indications for opening the duct, but in the remaining case there was no clinical or operative evidence which favoured the presence of a stone.

In recent years several series of cases have been published which analyse the "post-cholecystectomy" syndrome, and it is clear that in most series a residual stone has played the leading part (Gray and Sharpe, 1944; Adams and Stranahan, 1947; Millbourn, 1950). Stones even when quite large often cannot be felt, and to detect these the surgeon must rely on less satisfactory indirect evidence such as a pre-operative history of jaundice, or the operative discovery of a dilated, thickened common bile duct, especially if it contains thick muddy bile, a gall-bladder filled with small stones, a widened cystic duct, and a thickened pancreatic head. The significance attached to such indirect evidence varies widely, so accounting for the discrepancy in the frequency with which the duct is explored by individual surgeons.

If the surgeon explores the common bile duct in all cases in which there is some evidence of a common bile duct stone he will find that diagnostic operative cholangiography is of little value. Whilst small stones and even large ones might easily be overlooked by the most experienced surgeon, in the wet *x*-ray films of diagnostic operative cholangiography they may likewise pass unnoticed, for the most enthusiastic protagonist of operative cholangiography will not claim for it an accuracy of more than 95% (Mixter *et al.*, 1951).

Apparent Advantages of Control Operative over Post-operative Cholangiography

When the common bile duct is opened and drained it is common practice in the post-operative period to take an *x*-ray film of the biliary tract after injecting an opaque medium down the tube to test the patency of the duct. If such a post-operative cholangiogram discloses an overlooked stone in the common bile duct the surgeon is placed in a difficult position, because a second operation at this stage can be undertaken only with great reluctance.

In nearly one-third of the patients who died after removal of stones from the common bile duct stones still remained in the ducts at necropsy (Mayo, 1923). Hicken *et al.* (1950) and Mixter *et al.* (1951) claimed that cholangiograms performed a week after operation showed the average incidence of missed stones to be approximately 10%.

In the present series control operative cholangiograms were performed in 10 cases and an overlooked stone was found in one of them; it was a relatively simple matter to re-explore the duct at the time and remove the stone. Although interpretation of the films presents difficulties, in view of the impossibility of ensuring removal of all the stones after exploration of the common bile duct a control operative cholangiogram is useful and should certainly replace the post-operative cholangiogram with its restricted value.

Recognition of Disorders of the Biliary Tract Coexisting with Gallstones

Archibald (1919) suggested that spasm of the sphincter of Oddi might be responsible for acute pancreatitis, and Westphal (1923) published a classification of sphincter disorders based on a series of experiments performed on animals; functional disorders of the sphincter have since been held responsible for some of the poor results of cholecystectomy. Mirizzi (1948) and Mallet-Guy *et al.* (1947) have reported numerous instances in which operative cholangiography has demonstrated to their satisfaction sphincter spasm or sphincter atony of a degree sufficient to produce symptoms.

In the present series there was but one instance in which it appeared that the sphincter was in a state of spasm, although apparently this was of no consequence. Functional disorders of the biliary tract rarely call for operative treatment at the Royal Melbourne Hospital, where 97% of the gall-bladders removed contain gall-stones; even the remaining 3% can usually be explained on pathological grounds other than sphincter incoordination.

The diagnosis of ampullary stenosis should likewise be made with caution. Normally both the common bile duct and the pancreatic duct of Wirsung narrow abruptly where they meet just outside the duodenal wall (Hughes and Kernutt, in press); and they course together through the duodenal wall for a distance of up to 25 mm.: it is here that the cholangiogram often conveys a false impression of a long narrow stricture.

Operative cholangiograms direct special attention to the common bile duct, and for this reason lesions existing in conjunction with gall-stones might be demonstrated. In the present small series of cases this has not proved to be the case, probably because of the rarity with which such lesions occur.

Conclusions

As a diagnostic aid operative cholangiography has proved on the whole disappointing, and in view of the negligible added risk of exploring the common bile duct it is unlikely to be widely adopted. In obstructive jaundice and in cases in which the common bile duct required a second exploration, operative cholangiography can be recommended as an important step in elucidating the sometimes confusing pathology.

In view of the difficulty of ensuring complete removal of all the stones from the common bile duct in cases of choledocholithiasis, and because of the very limited practical value of post-operative cholangiography, a control operative cholangiogram performed at the conclusion of the operation but before suturing the abdominal wall is useful.

No operative cholangiogram in this series has demonstrated definite coexisting disturbance in the function of the sphincter of Oddi.

Summary

Operative cholangiograms were carried out by us in a series of 50 patients. "Diagnostic operative cholangiogram" was the term applied to the film taken just before the dissection on the biliary tract was begun, while "control operative cholangiogram" referred to that taken after the duct had been explored but before closure of the abdomen.

The method employed involved the insertion of a ureteric catheter into the common bile duct. A solution of diodone ("pyelosil 35") was the medium used. Satisfactory films were obtained in 45 cases; in the remaining 5 a second film was necessary.

In 32 instances the cholangiogram appeared normal; In 12 cases stones were visualized as filling defects and removed. In three cases no dye entered the duodenum, and in two of these stones were removed from the common bile duct. In 13 of the 14 instances in which stones were found indications for opening the common bile duct were present. The operative cholangiogram appeared abnormal in three further cases but no stones were found on exploration.

Control operative cholangiograms were taken in 10 cases and in one an overlooked stone was discovered; the duct was thereupon re-explored and the stone removed.

In one case no dye entered the duodenum and no stone could be found responsible.

It is concluded that while diagnostic operative cholangiography has proved disappointing as a routine procedure it may assist in elucidating the pathology in obscure cases of obstructive jaundice and in patients with recurrent symptoms following cholecystectomy. Control operative cholangiography is much more useful than post-operative cholangiography.

We are indebted to Mr. G. R. A. Syme for making available so many beds during the course of this investigation; and to Mr. Syme and to Mr. Orme Smith for much valuable advice. We acknowledge the assistance of Dr. Barbara Wood and Dr. Keith Hallam, of the Radiological Departments of the Royal Melbourne Hospital and Bethesda Hospital, Melbourne, respectively.

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PATHOLOGICAL CHANGES IN THE LIVER IN SALM. TYPHI-MURIUM INFECTION

BY

E. J. S. WOOLLEY, O.B.E., M.R.C.P.

Physician, Derbyshire Hospital for Sick Children

Damage to the liver in the course of illness resulting from infection by organisms of the *Salmonella* group is not usually so severe as to affect the clinical picture, and gross morbid changes are not described. Saphra (1950) collected 3,279 cases of salmonella infections. These included 174 deaths, 63 of them due to *Salm. typhi-murium*. No mention was made of any hepatic lesions. Guthrie and Montgomery (1939), in describing a series of cases of *Salm. enteritidis* infections, reported in their post-mortem findings only "the usual toxic changes" with cloudy swelling, fatty degeneration, and the absence of focal necrosis in the liver. Nasso (1947) reported two cases of infection by *Salm. cholerae-suis* which showed jaundice and enlargement of the liver and spleen. Giaccai and Idriss (1952), in a case of osteomyelitis due to *Salm. enteritidis*, noted jaundice during the illness. Their case also showed enlargement of the liver and spleen and there was anaemia requiring transfusion. Ashby and Wright (1905) quote a case in which cirrhosis occurred in a child who had suffered from clinical typhoid fever. Ascites, enlargement of the spleen, and anaemia began ten months after the acute illness. At necropsy a small hobnail liver was found. The bacteriology and morbid histology were not reported. In babies dying in an epidemic due to *Salm. oranienburg*, Epstein *et al.* (1951) demonstrated changes in the liver ranging from fatty degeneration to scattered foci of necrosis with oedema. Their illustrations show collections of myeloid cells in the portal spaces.

In the following case a clinical portal cirrhosis occurred in the course of an illness due to *Salm. typhi-murium*.

Case Report

A girl aged 1 year and 9 months was admitted to hospital on March 6, 1951. Two weeks before admission she developed bronchopneumonia. The signs in the chest cleared but the temperature did not fall. She lost weight rapidly and became severely ill.

On admission she was drowsy, dehydrated, and toxic; her temperature was 105.2° F. (40.7° C.). The abdomen was slightly distended and doughy. The liver and spleen were not felt. Her weight was 17 lb. 6 oz. (7.9 kg.) and her length 30 in. (76 cm.). The stools were profuse and fluid. The white-cell count was 9,300—28% neutrophils and 32% old metamyelocytes. Blood culture grew *Salm. typhi-murium*, and the same organism was recovered from the stool. The urine was physiological.

She was treated with chloramphenicol for 15 days. In three days the temperature was normal, the blood culture was sterile, and pathogenic organisms had disappeared from the stool. One week after stopping treatment the temperature rose again and the organism reappeared in the stools, but the blood culture remained sterile. This relapse was the first of a series each associated with a high temperature and illness. The relapses were treated with chloramphenicol, aureomycin, and streptomycin, alone and in pairs, and on one occasion with oxytetracycline. Courses of treatment were continued for periods of up to four weeks. Initially she responded well, but gradually it became difficult to control the pyrexia. After six months the temperature remained persistently raised in spite of treatment, and a state

of clinical resistance to chloramphenicol, aureomycin, and streptomycin had been established. Further supplies of oxytetracycline were not available at that time. The organism was regularly recovered from the stools.

The *liver* was first felt one week after admission; it increased steadily in size, the lower border reaching the umbilicus by December, 1951. The *spleen* was not felt until December, 1951. The enlargement was less rapid than that of the liver, and it did not reach the level of the iliac crest until November, 1952. *Ascites* appeared in December, 1951, and required repeated paracentesis. Dilatation of the *superficial veins* occurred gradually during the first six months of 1952 and *oesophageal* varices were demonstrated radiologically in August, 1952. Anaemia of hypochromic type developed gradually and transfusion was necessary at intervals of from three to six weeks during the period July, 1951, to February, 1953. Haematemesis, epistaxis, haematuria, and the presence of occult blood in the stools occurred repeatedly during the latter months of 1952. At the same time the child developed a thrombocytopenia and prothrombin activity fell to 10%, rising after the adminstration of "synkavit" to 30%. At no time was the child jaundiced. During the period March, 1951, to February, 1953, she did not grow, and her weight varied between 17 and 23 lb. (7.7 and 10.4 kg.).

In January, 1953, she was again given oxytetracycline. The dosage was at the rate of 100 mg. per kg. There was an immediate improvement. The temperature fell to normal, the appetite returned, and she became active and vivacious. The anaemia improved and the platelet count rose to normal.

After a month streptomycin was substituted for oxytetracycline. Clinical relapse occurred within a week. From February, 1953, onwards the child continued to take oxytetracycline and remained well. In June, 1953, her weight was 31¼ lb. (14.3 kg.), height 33 in. (84 cm.). The liver and spleen were both enlarged 4 in. (10 cm.) below the costal margins and there was still some ascites.

Investigations.—The results of some laboratory investigations which may be relevant to the pathological changes in the liver are shown in the Table. The *white-cell count* varied between 6,900 and 20,000, but was usually low. There was always a shift to the left in the neutrophil series. The *bone marrow* was normal in December, 1951, and in August, 1952. In January, 1953, there was moderate hypoplasia of the red-cell series, a slight myeloid reaction, and some increase in the number of megakaryocytes. The *urine* throughout the illness has shown varying amounts of albumin and an occasional granular and hyaline cast. Red cells were present during the periods when bleeding was occurring. The *blood urea* remained within normal limits. The *faeces* always contained *Salm. typhi-murium* except for a short period during the treatment with oxytetracycline, when a profuse growth of *Proteus vulgaris* masked all other organisms.

Laboratory Investigations

	December, 1951	July, 1952	January, 1953
Thymol:			
Turbidity	25 units	48 units	31 units
Flocculation	++++	++++	++++
Alkaline phosphatase (King–Armstrong)	19·2 units	30 units	41·5 units
Plasma proteins:			
Total	5·9 g.%	6·4 g.%	6·5 g.%
Albumin	3·3 g.%	3·9 g.%	3·4 g.%
Globulin	2·6 g.%	2·5 g.%	3·1 g.%
Blood cholesterol	176 mg./100 ml.	157 mg./100 ml.	106 mg./100 ml.
Van den Bergh	Negative	Negative	Negative
E.S.R. (1st hour)	48 mm.	74 mm.	45 mm.

In April, 1951, the serum agglutinated a suspension of non-specific salmonellae at a dilution of 1:640. In August, 1952, the agglutination of *Salm. typhi-murium* by the patient's serum was: "O"+, 1:20; −, 1:40. "H"+, 1:4,000; −, 1:4,500.

Liver Biopsies.—The first operation for biopsy was carried out under general anaesthesia on January 23, 1952. Sections showed a polymorphonuclear inflammatory reaction in the portal tracts, and much fibrous tissue. There was an apparent increase in the number of bile capillaries. Mitoses were not seen, however, and it is probable that the appearance was due to crowding together of the bile ducts as the result of the loss of intervening liver tissue. The material in the bile ducts consisted of masses of Gram-negative bacilli (Figs. 1 and 2). The second biopsy was carried out on July 23, 1952.

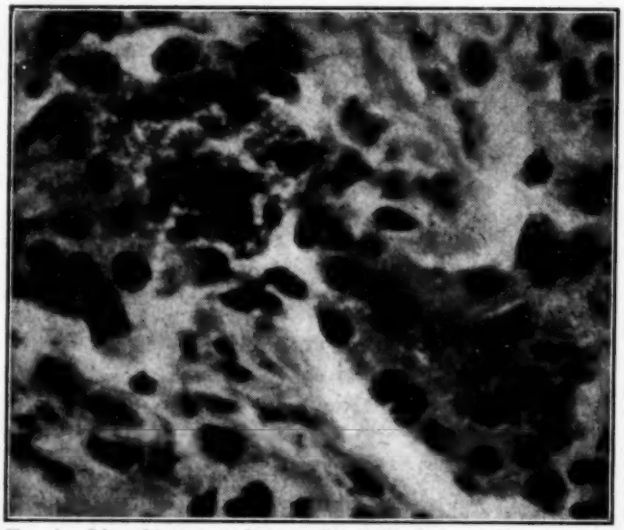

FIG. 1.—Liver biopsy on January 23, 1952, showing fibrous tissue and polymorphonuclear cells surrounding bile ducts packed with bacteria. (H. and E. ×750.)

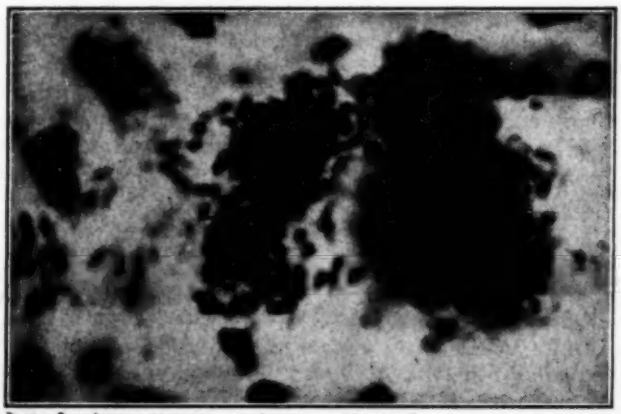

FIG. 2.—Liver biopsy on January 23, 1952. Masses of Gram-negative bacilli in the bile ducts. (Gram. ×1,440.)

an attempt to measure the portal venous pressure was unsuccessful because of the enormous size of the liver and spleen. The sections from the liver showed an increase in both the degree of inflammatory reaction and the extent of the cirrhosis. Organisms were again seen in the bile ducts, but were fewer than at the previous biopsy. Culture of a piece of liver gave a pure growth of *Salm. typhi-murium*.

Discussion

The pathological findings in this case are unlike the lesions described in typhoid fever, which consist typically of foci of necrosis in the lobules as the result of sinusoids being blocked by macrophages.

It is known that liver damage can be caused by aureomycin and oxytetracycline, but probably only when these drugs are given parenterally as well as orally (Lepper *et al.*, 1951). The clinical picture in such cases includes jaundice, and the morphological change consists of severe vacuolation and disintegration of cytoplasm, particularly near the

central vein of the lobule. These findings were absent in my patient and neither of the incriminated drugs had been given by injection.

Cirrhosis can occur as the result of impaired intestinal absorption in chronic disease in the bowel. Dyson (1950) reported three cases of long-standing ulcerative colitis in which a fine portal cirrhosis was found. There was also a necrosis of liver cells in the central areas of the lobule. In the case reported here there was no evidence of impaired absorption from the bowel, and the liver damage was essentially peripheral.

Cameron *et al.* (1940) produced morbid changes in the livers of rats by the intraperitoneal injection of a toxic fraction derived from *Salm. typhi-murium*. The changes included congestion of the portal vein and a peripheral necrosis of the hepatic lobule.

The observation of the organisms in the intrahepatic bile ducts is important, and suggests that the gall-bladder, which has been regarded as the main reservoir of infection in carriers of salmonellae, may play only a secondary part.

The partial suppression of the organism by treatment altered the normal course of the illness in this case. This child would probably have died if antibiotics had not been given. She was allowed to live long enough for the salmonellae surviving in her bile ducts to cause an inflammatory reaction, with destruction of liver tissue and the development of cirrhosis.

Bacteriology

The antigenic structure of the organism obtained from the liver was O=IV, V, XII; H=i—1, 2, 3.

In vitro the organism cultured from the stools was consistently resistant to penicillin but sensitive to 2.5 μg. of streptomycin and to 25 μg. of chloramphenicol per ml. Sensitivity to 1:1,000 sulphathiazole was reported once in November, 1952, but on all other occasions the organism was resistant. The sensitivity to aureomycin was not constant. It varied from complete resistance to 25 μg. to moderate sensitivity to 10 μg. There was resistance to 10 μg. of oxytetracycline in November, 1952, weak sensitivity in January, 1953, and sensitivity in March, 1953. These *in vitro* assessments of the sensitivity bore no relation to the clinical results obtained. Chloramphenicol, aureomycin, and streptomycin were clinically useless after the first six months of the illness. Oxytetracycline produced a spectacular clinical improvement at a time when the organism was showing only weak sensitivity. A similar discrepancy between the effect of antibiotics *in vivo* as compared with the sensitivity of the organisms *in vitro* was noted by Epstein *et al.* (1951) in infections due to *Salm. oranienburg*. The discrepancy may be related to the varying extent to which the antibiotics are excreted in the bile. Welch (1950) showed that, following test doses, chloramphenicol appeared in the bile of rabbits in a higher concentration than aureomycin or oxytetracycline, while in human beings the concentration of oxytetracycline in the faeces was higher than that of either of the other two. In this case the effects of antibiotics on the bacteria in the bile ducts would be reduced as the result of the isolation of the organism from the blood stream by fibrosis and the absence of a flow of bile through the ducts following the destruction of liver tissue.

Summary

A case is described in which cirrhosis developed in a child suffering from a chronic *Salm. typhi-murium* infection.

The cirrhosis was confirmed by liver biopsies.

The living organism was demonstrated in the intrahepatic bile ducts 16 months after the onset of the illness.

The sensitivity of the organism to antibiotics *in vitro* was inconstant and did not correspond with the clinical effects of the drugs.

My thanks are due to Dr. G. R. Osborn for his help and advice in the study of this patient; to Mr. A. J. Wilson, who performed the biopsies; to Dr. Joan Taylor for the antigen structure of the organism; to the house-physicians at the Derbyshire Hospital for Sick Children; and to Mr. J. S. Fayers for the photography.

ADDENDUM.—Since this report was prepared for publication the child has died. Treatment with oxytetracycline was continued for a year. The child remained well and grew. The evidence of portal hypertension became less. Repeated culture of the stools failed to show salmonellae. Three months after stopping the drug there was a sudden relapse and she died. At necropsy the changes in the liver were essentially the same as those found during life, but there was acute inflammation of Peyer's patches. *Salm. typhi-murium* was grown from the stools, from the gall-bladder, and from the liver.

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PRIMIDONE IN THE TREATMENT OF EPILEPSY

BY

J. B. LYONS, M.D., M.R.C.P.I.

Medical Registrar, Department of Neurology, Manchester Royal Infirmary

AND

L. A. LIVERSEDGE, M.D., B.Sc., M.R.C.P.

Lecturer in Neurology, University of Manchester

Handley and Stewart (1952) first reported the use of primidone ("mysoline"; 5-ethyl-5-phenyl-hexahydropyrimidine-4:6-dione) in the treatment of epilepsy, and since then a number of papers have appeared indicating the effectiveness of the drug in controlling epileptic manifestations of various types (Butter, 1953; Whitty, 1953; Smith and Forster, 1953). Many of the cases in these surveys—including that of Whitty (1953) and of Greenstein and Sapirstein (1953)—were given primidone in addition to other drugs. Nathan (1954), however, reports satisfactory results in 43% of 21 cases of symptomatic epilepsy treated with primidone alone. The present report deals with 44 cases of epilepsy of various types in which previous medication was completely replaced by primidone.

The 44 patients (19 male, 25 female) varied in age from 13 to 52, and were representative of the types seen in a neurological out-patient department. Handley and Stewart's patients were in an institution and so were possibly more refractory cases than the average epileptic not requiring institutional care. An adverse selective factor also operated in our series, since all the patients had failed to respond satisfactorily to other forms of treatment. The period of survey was 3–14 months, the majority of the patients having been followed for six months at least. The tabulated results deal with only 42 patients, as two were unable to continue their treatment for more than a few days. These 42 comprised the following clinical types: 3 post-

traumatic, 8 symptomatic, and 31 idiopathic. Five of the idiopathic group were of late onset, and, although as yet no underlying neoplastic or other structural lesion has been demonstrated, they may later prove to belong to the symptomatic group.

Primidone Dosage

The effective daily dose was found to vary from 0.5 to 2.5 g. daily, most cases requiring 1 to 1.5 g. a day in three or four divided doses. It has been suggested that the replacement of previous medication should be spread over a period of two or three weeks, but in this series the change was usually effected within one week. Our usual practice was to begin with primidone, 0.25 g. twice daily, overlapping the previous medication in full for two days. On the third and fourth days the primidone was increased to 0.25 g. thrice daily, and the previous medication reduced by half. On the fifth and sixth days the primidone was raised to 0.25 g. four times daily, the other drugs being abandoned on the seventh day. Thereafter the primidone dosage was decreased or increased according to need.

In five of the patients in whom the response to primidone was unsatisfactory, phenobarbitone or phenytoin sodium was added. We found, as had other observers (Whitty, 1953; Jorgensen, 1953), that the combination of phenobarbitone and primidone produced excessive drowsiness in relatively low dosage, whilst the combination of phenytoin and primidone did not have this soporific effect.

Results

The general effects of primidone treatment on the group are as follows (illustrated in Fig. 1). Of the 42 patients, 1 (2.4%) was made worse, 13 (31%) were unchanged, and 28 (66.6%) were improved. Taking the 28 who were

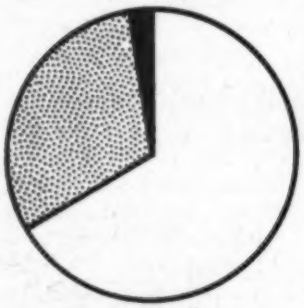

FIG. 1

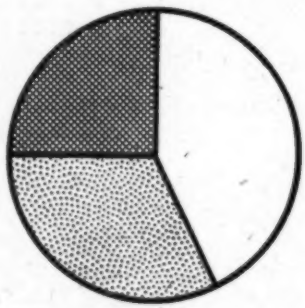

FIG. 2

FIG. 1.—42 cases. The white area shows the proportion improved; stippled, those unchanged; black, those worse. FIG. 2.—28 improved cases. White: complete relief. Stippled: 75% or greater reduction in attack rate. Hatched: 25%–75% reduction in attack rate.

improved, it is found that 12 (43%) had complete relief, 9 (32%) obtained a 75% or greater reduction in the number of their attacks, and 7 (25%) had an improvement estimated as between 25% and 75%. (These proportions are depicted in Fig. 2.)

Table I classifies the results obtained in relation to aetiology: 21 of the 31 idiopathic epileptics, all 3 traumatic, and 4 of the 8 symptomatic were improved.

Table II shows the analysis of the effect of primidone on the different types of attack. The broad deduction to be made is that some benefit may be produced irrespective of the type of attack, with the exception of the fact that no relief was recorded in the two examples of myoclonus. In one of these patients, a girl of 14, myoclonic jerks occurred as well as grand mal attacks. The grand mal was controlled by primidone, but the myoclonus was unaltered. The second patient, a woman aged 21, experienced frequent myoclonic jerks of the left arm and leg every day, which at times became severe enough to prevent her from going about. Ten months' treatment with primidone produced no improvement in the myoclonic jerks. She had very rare grand mal attacks, which constituted a minor problem in this case, since these had been well controlled by previous medication.

TABLE I.—*Results in Relation to Aetiology*

Type of Epilepsy	No. of Patients	Improved				Unchanged	Worse
		Complete Relief	75% or More Reduction	25% or More Reduction	Total		
Idiopathic ..	31	10	6	5	21	9	1
Traumatic ..	3	1	1	1	3	0	0
Symptomatic ..	8	1	2	1	4	4	0

TABLE II.—*Effect of Primidone on Various Types of Seizure*

Type of Seizure	Incidence	Improved				Unchanged	Worse
		Complete Relief	75% or More Reduction	25% or More Reduction	Total		
Major	24	9	5	5	19	5	0
Akinetic ..	4	1	1	1	3	1	0
Minor	3	–	1	–	1	2	0
Focal	10	2	2	1	5	5	0
Psychomotor ..	2	–	1	–	1	0	1
Myoclonic ..	2	–	–	–	0	2	0

Toxic Effects

Previous reports have indicated that primidone treatment does not produce any adverse effects upon blood formation or renal function. The side-effects produced in our series include drowsiness, anorexia, dizziness, unsteadiness, headaches, and dysarthria. Of these, drowsiness was the commonest, 14 of our patients being affected, though four of these added that the degree of drowsiness was less than that previously experienced with phenobarbitone. The drowsiness tends to disappear within two to three weeks, and, unless very severe, does not call for reduction of primidone dosage. Two or three patients have continued to complain of excessive drowsiness in the early mornings, although they have felt normal during the rest of the day.

Anorexia was reported three times, and in the two cases in which the drug was discontinued was associated with nausea, vomiting, and malaise as the reason for cessation of treatment. Slight unsteadiness occurred in four patients, vertigo in one, and headaches in three. Two patients had a little slurring of speech in the first week of treatment.

There seems to be little danger of serious overdosage. A case report in the German literature (Arnold and Ceranke-Höfermayer, 1953) deals with an unsuccessful suicidal attempt by a man who swallowed 120 tablets (30 g.) of primidone in five hours.

Electroencephalography

Whitty (1953) surveyed his results in relation to the type of electrical abnormality demonstrable on the E.E.G. pattern, and found that all types responded to primidone therapy in roughly the same manner. We have made no attempt to analyse our results in this way, but six cases had comparative electroencephalograms before and during treatment. The record showed a definite improvement in two of these patients who had obtained complete relief from attacks. One whose attacks were reduced by 75% or more had a similar improvement in the electroencephalographic pattern. Two others in whom the clinical improvement was assessed as 25% had no significant alteration in the pattern. In the sixth case, although no clinical improvement had occurred, the E.E.G. recording was also very much more normal. In all cases of epilepsy—treated and untreated—E.E.G. records tend to show variation, and it is not possible to make any definite deductions from this group. These findings are, however, in agreement with those of Andre-Balisaux and Devos (1953), who describe similar amelioration in the E.E.G. of five patients with focal temporal lobe abnormalities.

Conclusions

This survey offers further evidence of the value of primidone as an anticonvulsant agent. The drug may be used alone, and has produced a 75% or greater reduction in the number of attacks in 21 out of 42 patients, all of whom had been treated previously with other drugs with unsatisfactory responses. Should it be desired to combine primidone with other drugs, phenytoin sodium seems preferable to phenobarbitone. The severe toxic effects are negligible, and the symptomatic side-effects tend to be transient and rarely require discontinuation of treatment. If previous treatment has been given, substitution with primidone can be accomplished in one week, building up to the optimum average daily dose of 1 to 1.5 g.

The cases described were under the care of Dr. Fergus R. Ferguson, to whom we are further indebted for helpful advice and criticism.

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PRIMIDONE IN MENTAL DEFICIENCY PRACTICE

BY

D. S. SHARPE, M.R.C.S., L.R.C.P., D.P.M.

Senior Registrar, Botleys Park Hospital, Chertsey

That epilepsy is all too common a concomitant of mental deficiency is well illustrated by Tredgold (1952). He states that fits occur in 11% of the feebleminded, 42% of imbeciles, and 56% of idiots. Thus we who devote ourselves to the care of defectives should be on the alert for newer and better therapy for our epileptic patients. Encouraged, therefore, by the reported success of Handley and Stewart (1952) and Butter (1953), using primidone ("mysoline"), it was decided to give this drug a trial with a number of epileptic patients residing in Botleys Park Hospital for Mental Defectives.

Primidone, a stable white crystalline anticonvulsant with the chemical formula 5-ethyl-5-phenyl-hexahydro-pyrimidine-4:6-dione, was first reported on in this country in 1952 by Handley and Stewart. They showed good results amongst epileptics at the David Lewis Epileptic Colony. This report was followed by a similar paper by Butter, dealing again with patients in an epileptic colony. Whitty (1953) and Greenstein and Sapirstein (1953) have reported very comprehensively on a series of epileptics of varying types selected from out-patient practice of a neurological unit.

Clinical Trial

The aims of the trial were: (1) Primarily to discover whether grand mal epilepsy as found in the mental defective reacts favourably to primidone; (2) to observe changes, if any, occurring in petit mal, with especial reference to changes in the E.E.G.; (3) to discover whether there was any correlation between I.Q. and results, or age and results; (4) to observe and record any toxic effects.

It should be noted that all the patients concerned had grand mal epilepsy of varying degree. Some had behaviour disorders such as would permit classification amongst the psychomotor types. Others had accompanying petit mal; these were all investigated by electroencephalography, and only those who showed characteristic spike-and-wave phenomenon were included. These totalled only six cases owing to the fact that all too frequently the patient was found to be unsuitable for any attempt at electroencephalography. It is regretted that a more extensive investigation of the effect of this drug on behaviour disorders of the psychomotor type was not possible owing to necessary limitation of expenditure.

Method Employed

The number of cases selected was 38 (15 women, 15 men, 8 children). Their ages ranged from 7 to 52 years. Seven showed focal signs in the form of a hemiplegia and were therefore classed as traumatic. One case suffered from tuberous sclerosis. The I.Q. ranged from those who were inaccessible to 83 on the Wechsler scale.

Each subject acted as his or her own control. This was facilitated by referring to the epileptic charts recording the patient's previous attacks. Except in the case of some of the children, whose long-standing records were not available, at least three-years records were used in order to obtain a percentage of occurrence of attack prior to the survey.

The method of administration followed closely that used by Handley and Stewart. This consisted in adding 0.25 g. of primidone twice daily to the medicaments which the patient was receiving at that time. This continued for a week, when an additional 0.25 g. was given and at the same time gradual withdrawal of existing barbiturates was begun. During the third week a further 0.25 g. was added (the total being given in two daily divided doses). At this stage any other anticonvulsants such as phenytoin were also gradually withdrawn. The patients in this trial were therefore receiving only primidone, and this fact must be remembered when the results are assessed. In practice, an attempt was made to control the epilepsy with a daily dose of 1 g. of primidone. Where deterioration was serious, however, the dosage was increased up to 2 g. a day. It was found that the drug was well tolerated by children, and the average controllable dosage was about three-quarters that of an adult. As, however, the youngest child was aged 7, no assessment can be offered for infants or very young children.

It was thought advisable during the drug-substitution period to remove the barbiturates before any of the other anticonvulsants. This procedure was found to reduce any period of initial drowsiness which might take place. The total period of treatment with the drug was six months.

Toxic Effects

In common with the findings of other writers, primidone proved to be remarkably free from toxic effects of a serious nature. Drowsiness was a pronounced feature in about half of the cases initially, but soon became less so as the course proceeded. Ataxia was present in three cases, but in only one had the dosage to be reduced, and on a subsequent increase no further ill-effects were seen. Three patients became very confused and deteriorated mentally, and treatment was abandoned. No toxic skin rashes were reported. One patient developed a radial nerve palsy, but as there was a history of trauma, and as the condition subsequently cleared up without discontinuing primidone, it was thought to be coincidental to the treatment.

Results

Grand Mal Epilepsy.—The results in various age groups are given in Table I. The data are based on the percentage of grand mal attacks during the course of treatment in

TABLE I

Age Group in Years	No. of Cases	Discontinued	Worse −20%	No Change ±20%	Improved +20%	No Fits
5 to 15	10		T	XXX	XXXXT	X
16 to 25	13	XXT	XXXXT	X	XXXT	
26 to 35	3		X	X	X	
36 to 45	7		XX	X	EXT	T
46 to 55	5		XX	XX	X	
Total No. of Cases	38	3	11	8	14	2
Percentage Totals		7·9	28·9	21·1	36·8	5·3

X represents one case of grand mal epilepsy.
T represents one case of traumatic epilepsy as described in text.
E represents one case of tuberous sclerosis.

comparison with previous incidence before primidone therapy. "No change" is regarded as less than 20% improvement or deterioration. "Worse" is more than 20% deterioration. "Improved" is more than 20% improvement on previous attacks of fits. The other two columns are self-explanatory. Taking the last two columns as the sum total of all improvements, we find this to represent 42.1% improvement in grand mal epilepsy. The relationship between I.Q. and the results as shown in Table I can be seen from Table II. In order to simplify the records the I.Q.s have been divided into three sections corresponding to the three classic grades of mental deficiency.

TABLE II

	I.Q. Range		
	Less than 25	25 to 49	50 to 70+
Cases discontinued	3	0	0
Cases worse	4	4	3
Cases with no change	0	3	5
Cases improved	1	7	6
Cases with no fits	0	1	1
Total cases	8	15	15
% showing improvement	12·5	53·3	46·6

Petit Mal.—Only six cases of petit mal epilepsy were included in the investigation. All showed clinical signs of typical petit mal seizures, together with varying degrees of spike-and-wave activity as shown in the E.E.G. pattern. After approximately four months' treatment with primidone all these cases were re-examined by electroencephalography. The results showed that there was a deterioration in all cases; three had grossly deteriorated, and all six had a marked increase in spike-and-wave activity. In view of the recently described "temporal lobe epilepsy," it is perhaps of interest to state that two of the six cases showed abnormality arising from the temporal lobe. The repeat E.E.G. of these cases, though showing deterioration as already stated, demonstrated also in one case that the previously seen focal abnormality was not present. The results of the E.E.G., except in one case, agree with clinical observation.

Behaviour Changes.—No objective methods were used to demonstrate behaviour changes other than observation by the nurse in charge. In the case of the children included in this report, it was found that their behaviour had deteriorated. This appeared to be irrespective of any improvement of grand mal or otherwise, and they became generally much more difficult to manage. In one adult case, which could be classified amongst the psychomotor type, behaviour became very aggressive, and treatment had to be abandoned. Generally, however, amongst the adults little change in behaviour was noted.

Psychometric Assessment.—Wherever possible, all patients accessible to mental testing were investigated both before and after the course of treatment. The tests used were the Wechsler scale and the Goodenough drawing test. The results with the Wechsler scale showed that in seven cases clinically improved there was also some improvement in I.Q.—as much as 13 points in one instance.

Discussion

The above results show that in a series of 38 mentally defective patients of varying grades an improvement in epilepsy of the grand mal type occurred in 42.1%. These results seem to be poor compared with those of Whitty and, later, of Greenstein and Sapirstein, who showed 78% improvement in focal and grand mal epilepsy. One has, however, to consider two main factors in the comparison.

First, all the cases in the above two examples were from out-patient departments in neurological units. It is just possible that such patients were less likely to have deteriorated or to be liable to deterioration than the type of institutionalized mental defective. Secondly, in Greenstein and Sapirstein's work, only two out of 30 patients were treated with primidone alone. Similarly, Whitty used a combination of primidone with sodium hydantoinate. As already stated, primidone alone was used in our own cases.

In the light of these facts, and considering also the relative lowness of I.Q. in the present series, a net result of 42.1% improvement is thought to be creditable. These results follow more closely those of Butter, who, in a series of 58 cases, found that 50% derived benefit and in only 3% were fits abolished. It would seem from the works already quoted that the improvement obtained might well have been greater if a combination of drugs had been used.

From Table I there appears to be little correlation between age groups and results, except perhaps a tendency for the children aged 5 to 15 years to show more improvement. It is therefore tentatively suggested that in primidone may be found the anticonvulsant of choice in the initial therapy of grand mal epilepsy occurring for the first time at an early age.

In considering Table II it is significant that in the class with an I.Q. of less than 25 there was much less total percentage improvement. Thus it is evident that patients of low I.Q. will be likely to respond least favourably to treatment with primidone.

That primidone is relatively free from toxic effects is again demonstrated, and it may therefore be safely used in domiciliary practice.

The effect of primidone on petit mal seizures appears from a clinical point of view to be almost uniformly bad. This observation is given support by the results of the E.E.G. examinations on termination of treatment. This is in agreement with the findings of Greenstein and Sapirstein, who quoted two cases of petit mal, both of which had a marked increase in the number, frequency, and severity of the attacks.

Though, as stated, no pure case of psychomotor epilepsy was treated, from observations of the main group little change in behaviour is to be expected.

The improvement in I.Q. reported in seven "improved" cases is not thought to be due primarily to the action of primidone on cerebral intellectual functions. Surely it is due to the removal of some of the elements of clouding and confusion of the consciousness so often evident in the chronic epileptic. They thus become more accessible to mental testing and show corresponding rise in I.Q.

Summary

A series of 38 cases of mental defective epileptics treated with primidone is recorded.

Results showed that in grand mal epilepsy 36.8% were improved, and 5.3% were much improved in that fits were abolished.

Six cases of petit mal showed very poor results, both clinically and also in E.E.G.

The dosage of primidone used varied from 0.5 to 2 g. daily according to age.

Toxic symptoms very few—mainly drowsiness and some ataxia.

In three cases treatment was discontinued owing to confusion and to deterioration of the epilepsy.

I wish to thank Dr. J. M. Crawford, physician-superintendent of Botleys Park Hospital, for his help and encouragement with the above report; Dr. J. Carse, physician-superintendent of Graylingwell Hospital, Chichester; Dr. Parsons-Smith and the staff of the E.E.G. department there for carrying out the necessary E.E.G. investigations; and Miss F. K. FitzPatrick and the nursing staff of Botleys Park Hospital for their invaluable help. I acknowledge with gratitude the financial support given by the Research Subcommittee of the South-west Metropolitan Regional Hospital Board, without which the survey could not have been undertaken.

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USE OF POLYMYXIN B IN THE EXTERNAL EAR

BY

D. A. T. FARRAR, M.B., F.R.C.S.
E.N.T. Registrar, St. Bartholomew's Hospital, London

The polymyxin antibiotics were first described by Benedict and Langlykke (1947) and by Ainsworth *et al.* (1947). A series of antibiotic agents derived from *Bacillus polymyxa* have now been isolated and described; they are called polymyxins, and are differentiated by letters of the alphabet. The action of the polymyxins so far described—A, B, C, D, and E—seems to be bactericidal, and they all have similar antibacterial spectra, without significant differences (Brownlee *et al.*, 1952). *In vitro* experiments (Brownlee *et al.*, 1949; Pulaski *et al.*, 1949) have shown that they are effective against most Gram-negative organisms, in low concentrations. *Proteus vulgaris*, however, is an exception, and, together with the Gram-positive organisms, is sensitive only to high concentrations.

The polymyxins, chiefly B and E (the least toxic), have been used clinically, mainly by parenteral routes, in various infections due to Gram-negative organisms; the chief drawback to their use is their toxicity. A few workers have reported the use of these substances locally with some success (Jackson *et al.*, 1951; Jawetz, 1952). There do not appear to be any reports of a series of aural infections treated locally. There have also been no reports of any sensitization reactions after local use.

Present Series

Infections of the external auditory meatus, and in this group are included infected mastoid cavities, are often due to Gram-negative organisms. These infections are troublesome, since the organisms, particularly *Pseudomonas pyocyanea*, are often resistant to the commonly used antibiotics. A series of cases of otitis externa and infected radical mastoidectomy cavities have therefore been treated with polymyxin B locally. The cases chosen were those in which the infecting organisms were found to be one of the three chief Gram-negative types found in this region, *Ps. pyocyanea*, *Pr. vulgaris*, and *Bact. coli*. Infections caused by mixed organisms were not included.

The preparation used was a solution of 10% polymyxin B sulphate in propylene glycol, acidified with acetic acid. It was supplied to the patients in a bottle, with a dropper, for use at home. They were instructed to fill the ear with the solution, placing the head on one side, with the affected ear uppermost, morning and evening, and then to insert a plug of cotton-wool. A swab was taken from the ear for laboratory examination before treatment was begun and another after seven days' treatment. In most cases in which organisms were sensitive the ear was found to be dry at the end of this period. The results are shown in the Table. In a small number of cases the infection was bilateral, and the infecting organisms were the same on both sides. In these cases the polymyxin solution was instilled into one ear and a control solution, consisting of solvent only, was instilled into the other. At the end of the seven-days period the control solution was stopped, a swab taken for culture, and treatment with the polymyxin solution begun. In no case did the control solution alter the infecting organisms. The number of cases suitable to act as controls is small. No sensitivity or reaction to the solution was noted.

Results

Organisms	Type	No. of Cases	Dry	Failed	% Dry
Pr. vulgaris	Otitis externa	8 (2c)	1	7	10
	Radical cavity	12	1	11	
Bact. coli	Otitis externa	7 (3c)	5	2	65
	Radical cavity	13	8	5	
Ps. pyocyanea	Otitis externa	11 (3c)	10	1	90
	Radical cavity	9	8	1	

c=Cases with bilateral infection in which a control solution was used in one ear.

It would seem that the polymyxin B solution is effective in a large proportion of cases against infections of the external ear caused by *Ps. pyocyanea*. To a less extent it may clear up infections caused by *Bact. coli*. It is ineffective against *Pr. vulgaris*. These results conform to the *in vitro* sensitivity of the organisms concerned, except that *Bact. coli* appears to be less effectively controlled in the ear than one might expect from its *in vitro* sensitivity. Since *Ps. pyocyanea* infections are often resistant to other antibiotics and other forms of treatment, it is suggested that polymyxin B sulphate solution has a place in their local treatment.

Summary

A series of cases are reported in which polymyxin B sulphate was used in the treatment of otitis externa and infected mastoid cavities.

Polymyxin B sulphate appears to be effective against infections caused by *Pseudomonas pyocyanea*.

I would like to thank Mr. F. C. W. Capps for his encouragement and help, and Mr. F. Prescott and the Wellcome Research Institute for their generous help and supplies of polymyxin B sulphate.

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The 1954 *Yearbook* of the British Standards Institution, recently published (12s. 6d.), lists the British Standards current at March 31, 1954, and gives a brief description of each. They cover every field of industry and technology, and the standards laid down may be concerned with design, physical properties, methods of testing, limit tolerances, and so on. Many articles commonly used in hospitals and laboratories are manufactured in accordance with these standards, which are agreed only after discussion with all the parties concerned. The British Medical Association is a member organization and appoints representatives to committees of the B.S.I. when a medical opinion is required. Individuals are also eligible for membership of the B.S.I., and particulars as well as the *Yearbook* may be obtained from it at 2, Park Street, London, W.1.

Medical Memoranda

Sickling and Malaria

It has been suggested (Allison, 1954) that the sickle-cell trait affords a considerable degree of protection against *P. falciparum*. Allison's results with inoculated malaria showed that sickling was an almost complete protection against infection. In the field, however, it has been found that this relationship does not always exist. For example, amongst the Jaluo, whose sickle-cell trait is 28%, malaria is highly endemic. Amongst the Nilotes of the Southern Sudan, where malaria is similarly highly endemic, the sickle-cell trait is less than 2% (Foy *et al.*, 1954).

PRESENT INVESTIGATION

We therefore decided to study the association between malaria and sickle-cell trait in two tribes on the coast of Kenya that have widely different sickle-cell trait rates. The investigation was carried out on 400 Duruma and 400 Kambe. These subtribes form two divisions of the Nyika tribe. The method used to determine the sickle-cell trait was that used by Foy *et al.* (1951) in their survey of the sickling rates in Kenya and the Southern Sudan. Malaria was examined by the usual thick and thin smear method, and checked by different observers.

Preliminary results for 302 Duruma and 220 Kambe are presented here. The numbers include both adults and children. Table I shows the number and incidence of the condition for the Duruma and Kambe. It is immediately

TABLE I

	Duruma	Kambe
Total examined	302	220
Sicklers	31 (10%)	75 (34%)
Parasites	185 (61%)	135 (61%)
Enlarged spleen	104 (34%)	95 (43%)

obvious that for the two groups the parasite rates are identical, but the percentages of sicklers are very different. The proportions with enlarged spleens are nearly similar, although the difference is statistically significant at the 5% level. It should be noted, however, that the higher percentage is for the tribe with the greater sickling rate.

Before we investigate the relationship between sickling and malaria in individuals we should discuss the assumptions upon which tests of associations are based. This is necessary because too little attention has been paid to this subject in past surveys of this type, and we believe that this may have introduced major errors. The usual χ^2 test determines whether the characteristics are randomly related at any level of probability. If the random hypothesis is rejected, however, it does not follow that there is a genuine association for individuals. It is quite possible for associations to arise through fortuitous variations within the group studied. Thus, to take a simple case, if the sample consisted of two groups, each of which was homogeneous with respect to malaria and sickling, but the incidence of these two characteristics happened, by chance, to be higher in one group than the other, there would be an association which had no medical as opposed to statistical significance. If the sickling rate were constant throughout the population from which the groups were selected for study, such false associations could not occur, but it has been shown that variations in sickling exist, not only between tribes but even within tribes themselves (Foy *et al.*, 1954).

We believe that unless great care is taken in the design of a survey so as to eliminate these effects as far as possible, and unless the data are examined carefully from this point of view, there is a considerable chance that meaningless associations will be discovered.

The present survey was restricted to two small areas, and the homogeneity of the data was tested by studying the results in small sets in the order in which they were collected. This method detects any non-random variation in the rates within the samples. These checks are not given in full here, but it was found that for the Kambe there were no appreciable non-random variations in rates, whereas with the Duruma there were such variations for sickling, malaria, and spleen rates. It should be noted that the Kambe are a small, geographically restricted tribe, while the Duruma are more numerous, more widely distributed, and more urbanized.

Sickling and Malaria Parasites.—Although there was a slight positive association introduced for the Duruma by the non-homogeneity of the data, it had no appreciable effect on the overall results (Table II). There is no indica-

TABLE II

	Duruma			Kambe		
	No. Examined	Sicklers		No. Examined	Sicklers	
		No.	%		No.	%
Parasites positive ..	185	22	12	135	45	33
„ negative ..	117	9	8	85	30	35
Total ..	302	31	10	220	75	34

tion here of any association between the presence of parasites and sickling, the slight differences in the percentages being well within the limits of sampling fluctuations. Table III compares the number of cases showing both sickling and parasite infection with the number expected on the "hypothesis of no association" by type of parasite. Where a double infection was found it is shown against each parasite. The differences between the number observed

TABLE III

Parasite	Duruma			Kambe		
	No. of Cases	Sicklers		No. of Cases	Sicklers	
		No. Expected	No. Observed		No. Expected	No. Observed
P. falciparum	144	14·8	17	54	18·4	16
P. vivax ..	16	1·6	3	30	10·2	9
P. malaria ..	7	0·7	2	21	7·2	8
Not identified	22	2·3	1	36	12·3	13

and expected are of no significance for any of the species of parasites.

Sickling and Enlarged Spleens.—The overall results are shown in Table IV. There is clearly no association for

TABLE IV

	Duruma			Kambe		
	No. Examined	Sicklers		No. Examined	Sicklers	
		No.	%		No.	%
Spleen enlarged ..	104	4	4	95	31	33
„ not enlarged ..	198	27	14	125	44	35
Total ..	302	31	10	220	75	34

the Kambe, but for the Duruma there *appears* to be a negative association between enlarged spleens and sickling. χ^2 (with Yates's correction for continuity) is 6.07, which gives a probability of about one in seventy of obtaining the difference by chance. When the data are examined in small sets, however, it is found that the low probability is introduced by the non-homogeneity of the sample. Thus, when the Duruma are broken down into sets of 30 Africans (with 32 in the tenth to include all examined) the distributions of the characteristics shown in Table V are found. It so happens that there is a very high sickling rate in the second set, and a very low proportion with enlarged spleens. When allowance is made for this (by considering sets 1 and 2 separately from the rest because of the low enlarged spleen rates, and then applying a combined test) it is found that the association is not statistically significant despite the result found above for the Duruma when the correction is not made.

Raper has shown that the Baganda show no effect of sickling on malaria, but obtained an association among a

TABLE V.—*Distribution of Characteristics in Duruma*

Set	Sicklers	With Enlarged Spleen
1	2	2
2	9	2
3	4	8
4	5	15
5	3	6
6	1	11
7	—	12
8	3	14
9	2	14
10	2	20

mixed group of other tribes. In view of what has been said above, it would not seem that it has yet to be established that this has much meaning.

In conclusion, it would appear from the results given above that there is no confirmation of the theory that there is an association of any magnitude, such as suggested by Allison, between sickling and malaria.

A paper is in course of preparation in which fuller details will be given.

R. A. MOORE, L.R.C.P.&S.I., D.T.M.&H.
W. BRASS, M.A., B.Sc.
HENRY FOY, Ph.D., D.Sc.

Nairobi.

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Superior Sulcus Tumour

A superior sulcus tumour producing the typical syndrome reported by Pancoast (1932) may be caused by a variety of space-filling lesions of which the least uncommon is carcinoma of the bronchus. The following case is an example of such a tumour, and is reported because of its unusual longevity.

CASE REPORT

A man aged 55 was admitted to hospital on April 3, 1945, complaining of dyspnoea and pain in the right chest. An area of consolidation was present in the upper third of the right lung. A course of sulphathiazole resulted in some improvement, but abnormal signs persisted and on July 9 he was transferred to a thoracic surgical unit. He had had rheumatic fever at the age of 15 and had always had a slight productive morning cough, which had become more persistent since Christmas, 1944. In February, 1945, he had been in bed for ten days with a febrile respiratory illness.

Physical examination showed a gaunt man with gross finger-clubbing; vital capacity 3,500 c.cm. There were signs of consolidation with cavitation at the right apex posteriorly. He produced 1–2 oz. (28–57 ml.) of mucopurulent sputum daily, but numerous examinations by film and culture revealed no tubercle bacilli. No malignant cells, actinomyces, or elastic fibres were seen. Bronchoscopy on July 12 revealed no abnormality apart from pus in the right bronchial tree. A chest radiograph on admission showed displacement of the trachea to the right, with an opacity in the upper zone of the right lung. On August 1 the radiologist reported an extension of the lesion and suggested neoplasm as the cause. Two attempts at bronchography did not reveal any bronchiectasis in the upper lobe segments, but the apical bronchus was incompletely filled. A diagnosis of possible carcinoma was made, and he was discharged home on October 13 with a recommendation to remain under observation, which he ignored.

He did not come for examination again until October 19, 1953, when he was referred to the orthopaedic out-patient department of the Bedford General Hospital with a six-months history of pain in the right shoulder and down the inner aspect of the right arm. Haemoptyses lasting a week had occurred nine months previously, and hoarseness had been noted for six months. His appetite was poor, lassitude marked, and he had lost a stone (6.4 kg.) in weight over the previous year.

On examination he was emaciated, had a right Horner's syndrome, restriction of right shoulder movement, and loss of power with wasting of the right arm accompanied by venous engorgement and trophic changes in the limb. A mass was palpable in the right supraclavicular fossa. Radiographs showed an opacity in the upper zone of the right lung and erosion of the neck of the third right rib and bodies of D 3 and 4 on the right side.

He was admitted to hospital for investigation and soon developed a spastic paraplegia with sensory loss below D 2. Laminectomy was performed on December 9, when the tumour mass was found to have involved D 2 and 3 and caused considerable cord compression. Pressure was relieved and radiotherapy was started. He recovered for a while, but succumbed to a respiratory infection and died on January 9, 1954.

At necropsy both lungs showed bullous emphysema and terminal bronchopneumonia. A soft white tumour occupied the upper part of the right lung, and this had invaded the cervical muscles and vertebral column, penetrating to the cord, and had obliterated the right cervical sympathetic chain. There was no demonstrable connexion with a main bronchus. Histologically the tumour was a highly keratinized squamous-cell carcinoma. No evidence of tuberculosis or other pathological condition was found in the upper part of the right lung except tumour tissue and emphysema.

COMMENT

Superior sulcus tumour is a relatively uncommon growth, 151 cases having been reported up to 1946 (Herbut and Watson, 1946) and several since then, not all of which had been confirmed histologically. The survival time of these cases is usually short, the average time being about ten months from the onset of symptoms; this is four months less than the average for untreated bronchial carcinoma in other sites. Certain treated cases have, however, been reported with longer survival times: Haas *et al.* (1954), at least three and a half years; Chardack and MacCallum (1953), at least two and a half years; while Malcolmson (1947) recorded a case in which the diagnosis of lymphoblastoma in the apex of the lung was made at the Mayo Clinic and the patient lived for 18 years after *x*-ray therapy.

Untreated cases of bronchial carcinoma in any site which survive longer than eight years are themselves uncommon. Several authors report individual cases, the majority taking as their onset the development of definite signs or symptoms. Such durations are obviously open to question, as unequivocal diagnosis may not be obtained until very much later, but a few cases have been reported in which the patients have survived several years after definite diagnosis.

The case reported here was not confirmed histologically as a bronchial carcinoma in 1945, but there has been very little *x*-ray change in the right apical opacity during eight and a half years. The absence of tubercle bacilli on repeated examinations and the absence of any histological evidence of tuberculosis or chronic inflammatory condition, save terminal bronchopneumonia, in the right lung suggest that this was a case of peripheral carcinoma which had a long "silent period" in its development. It would be surprising, moreover, in this case for a neoplasm to arise, in the months prior to death, in an area of pulmonary fibrosis and to invade that area so exactly as to show almost no change on *x*-ray examination.

In view of the lasting radiographic evidence and post-mortem findings it is reasonable to suggest that this man had a tumour for at least eight and a half years before death.

I wish to thank Dr. N. Wynn-Williams for permission to publish this report.

R. DOUGLAS YOUNG, M.B., M.R.C.P.Ed.,
Assistant Chest Physician, Bedford Chest Clinic.

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Asthma Induced by Antihistamines

The phenomenon of rapid alternation of clinical syndromes among allergic individuals has long been recognized—for instance, asthma and eczema in young children. It would appear that the antihistamines are capable of provoking such an alternation. Tomlinson (1948) and Harris (1948) cite cases in which eczema supervened when hay-fever was treated with diphenhydramine hydrochloride. Frankland (1949) refers to the onset of asthma towards the end of the pollen season in patients who have been treated with antihistamines.

The records of nine patients who exhibited this phenomenon are given below. They were seen during the course of investigation and treatment of 3,000 cases of allergic rhinopathy (including hay-fever) in the past four years. In each case cited antihistamine therapy produced relief of the symptom treated, coincidentally with the appearance of asthma. In most cases this effect was reversible, and cessation of this therapy restored the *status quo ante*. Pollen was usually but not invariably a major aetiological factor.

CASE REPORTS

Case 1.—A woman aged 37 had had intermittent vasomotor rhinitis for 13 years; it was perennial, but worse in the summer months. Skin sensitivity to house dust and pollens was demonstrated. A first and only attack of asthma occurred with great severity immediately after taking antazoline tablets. This has not recurred, and the patient has refused to take further antihistamines.

Case 2.—A girl aged 8 had had atopic eczema since infancy and seasonal hay-fever for the last three summers, but no asthma. In the summer of 1950 she took mepyramine maleate on two or three occasions, and each time an attack of asthma supervened. When the drug was discontinued no further asthma occurred. Skin sensitivity was demonstrated to pollens only.

Case 3.—A woman aged 29 had had vasomotor rhinitis and asthma for five years. After a course of hyposensitization treatment in 1948 and 1949 the asthma had practically disappeared, but the vasomotor rhinitis persisted though improved. In April, 1950, she took promethazine hydrochloride for the first time, with immediate improvement of the nasal condition, but severe asthma occurred within three days. Cessation of the drug brought about complete relief of asthma but recurrence of vasomotor rhinitis. She has repeated the test on four further occasions (using different antihistamines) with identical results each time—on the third night of treatment she develops asthma.

Case 4.—A woman aged 30 had had morning rhinorrhoea for many years which cleared completely during pregnancy three years ago but recurred with increased severity and frequency a year later. Mepyramine maleate relieved the nasal condition, but within a day or two produced moderately severe asthma for the first time. The asthma has persisted in a mild form though antihistamines have been discontinued. Pollen sensitivity was demonstrated.

Case 5.—A woman aged 50 had seasonal hay-fever at age 21 which was treated and relieved by cauterization. A severe recurrence in the summer of 1949 was treated with diphenhydramine hydrochloride. Her first attack of asthma occurred immediately thereafter and has persisted in spite of cessation of antihistamines. Although pollen sensitivity can be demonstrated the asthma is not purely of allergic origin, as there is an infective element superimposed.

Case 6.—A woman aged 40 had a ten-years history of vasomotor rhinitis. In 1950 she was given promethazine hydrochloride, which afforded relief. Asthma then appeared for the first time—possibly coincidental. Sensitivity to house dust was demonstrated but not to pollens.

Case 7.—A woman aged 39 had had seasonal hay-fever for seven years, increasing in severity each year. It was twice aggravated by pregnancy. Three years ago a course of diphenhydramine hydrochloride was followed by relief of hay-fever, but the immediate appearance of asthma for the first time. Since then the asthma has recurred with each pollen season. Pollen sensitivity was demonstrated.

Case 8.—A woman aged 64 had had atopic eczema of the wrist and shoulders for 10 years. There was a family history of a similar complaint. On two occasions in 1949 she was treated with antazoline, and on each occasion immediately developed moderately severe asthma—her only two attacks. The causative allergen has not been identified.

Case 9.—A man aged 40 had a two-years history of perennial rhinopathy and nasal polyposis. He had mild wheezing in 1949 while taking promethazine hydrochloride. He was aspirin-sensitive. Skin sensitivity to pollens was demonstrated. Chlorcyclizine hydrochloride produced quite an acute attack of asthma, which disappeared with cessation of treatment but returned again when a further dose was taken.

COMMENT

The antihistamine drugs vary considerably in the relief they afford to different allergic manifestations. Good results are obtained in allergic rhinopathy, poor or negligible results in asthma, although Herxheimer has shown that histamine-induced bronchospasm or mild asthma can be relieved to a measurable extent by large doses of aerosol antihistamines. The theory has been put forward that in these resistant manifestations the histamine or H substance is released in a more inaccessible fashion, and that the neutralizing effect of antihistamine drugs fails to reach the point of release in adequate amounts. The series of cases described above could be explained by postulating that, an antihistamine having been given in sufficient dosage to neutralize an allergen-reagin reaction in one tissue, the reaction appeared in another tissue which the dosage administered was inadequate to protect.

D. BLAIR MACAULAY, M.B., M.R.C.P.,
Medical Officer in Charge, Allergy Clinic,
Liverpool Ear, Nose, and Throat Hospital.

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Optimum Injection Volume for Intramuscular Streptomycin Sulphate

Streptomycin sulphate has recently appeared on the market in solution ready for intramuscular administration, 1 g. being available as a 2, 3, or 4-ml. injection.

Our investigation was undertaken to determine whether the volume of fluid had any bearing on the pain-producing qualities of the injection. Only if a larger volume can be shown to be less painful is there any point in using it, for the advantages of 2-ml. injections in convenience and lesser cost of syringes are obviously great, particularly in domiciliary work. The viscosity rises so rapidly with smaller volumes of solvent that anything less than 2 ml. is impracticable.

METHOD

To ensure that any difference found would be due to the volume used and not to variations in the streptomycin or the solvent, only one manufacturer's materials were employed, the solutions being prepared specifically for the trial to exclude batch variations, etc.

A new No. 1 serum needle was used for each injection, this being the smallest needle offering little resistance to the flow of the more viscous 2-ml. injection. So far as was possible these injections were given by the same nurse (80%), and in any case one nurse gave all the injections on any one day. The injections were given alternately in the lateral aspect of each thigh, and the patients were unable to see the size of the syringe used.

Two separate trials were held, with an interval of one month between them. The patients were unselected, all who were receiving one daily intramuscular injection of 1 g. of

streptomycin being included. The interval enabled a greater number of patients to be included, for only three were in hospital long enough to appear in both trials. In the first trial seven men and six women were given a total of 180 injections. In the second trial six men and seven women received 149 injections.

The nurse giving the injections worked strictly to a prearranged plan, allocating 2 ml. or 4 ml. on a random basis. Only she knew the type of injection the patient had received.

One of us (L. C. K.) investigated on the following day the pain reactions of all the patients. Like them, the observer did not know which injections had been given, whilst both results and injection volumes were so recorded that only later could they be fully correlated. On three occasions it was not possible to record the results because the patients concerned were not fit to give a true record of the pain experience.

Pain reactions were classified as "immediate" and "delayed," with three arbitrary grades in each group (1=nil or mild; 2=moderate; 3=severe).

RESULTS

The results are shown in the Table. It will be seen that there are many more moderate and severe delayed reactions associated with 4-ml. than with 2-ml. injections. The pattern

Results

	Size of Injection	Degree of Pain 1	2	3	Total
Trial I (180 *Patients*)					
Initial pain	4 ml.	70	12	6	88
	2 ml.	76	14	2	92
Delayed pain	4 ml.	67	14	7	88
	2 ml.	82	8	2	92
Trial II (149 *Patients*)					
nitial pain	4 ml.	64	10	3	77
	2 ml.	67	3	2	72
Delayed pain	4 ml.	58	12	7	77
	2 ml.	61	9	2	72

is the same in each trial, which adds further significance to the results. In both trials combined, 40 moderate and severe delayed reactions occurred with 4-ml. injections as compared with only 21 with the 2-ml. injections ($\chi^2=8.62$, $P<2\frac{1}{2}\%$). The results for initial pain, although showing a similar trend, are not statistically significant.

CONCLUSIONS

If 1 g. of streptomycin sulphate is administered intramuscularly as a 2-ml. injection, significantly less delayed pain can be expected compared with its administration as 4 ml. Rising viscosity prevents less than 2 ml. being used, but this volume is satisfactory when using a No. 1 serum needle.

Streptomycin sulphate, now marketed as a prepared 2-ml. injection, is thus the most convenient and satisfactory form available. At the same time this packing minimizes handling by the nursing staff, and, if the rubber-capped vials are used, enables the officially recommended precautions against skin sensitization to be carried out. (Packing in a glass ampoule makes this impossible.)

Our thanks are due to Mr. N. W. Please for examining the statistical validity of our results; to the nursing staff and patients for their willing co-operation; and to Glaxo Laboratories Ltd. for preparing and supplying the streptomycin solutions.

PETER STRADLING, M.D., M.R.C.P.,
L. C. KREEGER, M.B., B.S.,
Hammersmith Chest Clinic and Postgraduate Medical School of London.

Metastases from Carcinoma of Bronchus causing Enormous Enlargement of Liver

The following case is reported on account of the enormous enlargement of the liver produced by metastatic tumour deposits.

CASE REPORT

A man aged 68 attended the Bradford Royal Infirmary on April 20, 1953, with a complaint of dyspnoea, abdominal swelling, and pain in the right upper quadrant of the abdomen of several weeks' duration. There was a history of productive cough during the past year and haemoptysis on several occasions during the previous three weeks. On examination he was very dyspnoeic. Palpation of the abdomen revealed a greatly enlarged and hard liver which was thought to be malignant.

On July 13 he was admitted to St. Luke's Hospital, Bradford. On admission (temperature 97° F. (36.1° C.), pulse 110, respirations 24) he was confused and dyspnoeic; there was neither cyanosis nor jaundice. Oedema of both legs and of the scrotum, penis, and sacral region was present. The abdomen was greatly distended and tender, and the lower border of what was thought to be the liver was palpable in the lower extremity of the abdomen. The breath sounds on the right side of the chest were diminished. He became progressively more confused and died on July 18.

Post-mortem Examination.—The relevant findings were as follows. At the hilum of the right lung there was a firm grey-white neoplasm, about 2 in. (5 cm.) in diameter, which appeared to originate in the main bronchus of the right middle lobe. There was no pneumonic consolidation. The liver was enormous (weight 19 lb. 4 oz. or 8,730 g.), and contained numerous metastases, ranging in size up to 4 in. (10 cm.) in diameter. The mediastinal, aortic, and upper abdominal lymph-nodes showed obvious metastatic involvement. The supraclavicular and axillary glands were not enlarged. The peritoneum, omentum, spleen, pancreas, adrenal glands, kidneys, and brain showed no macroscopical evidence of metastatic involvement. In the gastro-intestinal tract there was no evidence of a neoplasm. Five small superficial ulcers were present in the mucosa of the stomach along the greater curvature.

The histological features of the bronchial neoplasm were those of an undifferentiated carcinoma of "oat-cell" or spindle-cell type. The appearances were uniform throughout the primary growth and the metastases. The ulcers in the stomach were not neoplastic.

COMMENT

The noteworthy feature of this case is the size (8,730 g.; normal about 1,500 g.) of the liver. Cases in which livers with metastatic growths have attained great weights (13 between 5,000 and 10,000 g., and 7 exceeding 10,000 g.) are referred to by Willis (1952). The livers reported by Kikuth (1925) and Fried (1925) weighed 11,800 g. and 6,400 g. respectively, and were from cases of lung carcinoma.

In the above case the liver retained its normal shape despite extensive neoplastic involvement, and we are reminded that, next to local lymphatic spread, the liver is probably the most frequent site for metastases in carcinoma of the bronchus (Hadfield and Garrod, 1947; Willis, 1953).

I have to thank Mr. J. Dawson and Dr. C. L. Davidson for the clinical data relating to this case.

R. A. MCINROY, M.B., B.Sc., D.T.M.&H.,
Pathologist, St. Luke's Hospital, Bradford.

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Reviews

JOHN HUNTER'S ASSISTANT

William Clift. By Jessie Dobson, B.A., M.Sc. (Pp. 144+viii; illustrated. 21s.) London: William Heinemann Medical Books Ltd. 1954.

The genius of John Hunter was not fully appreciated by his contemporaries. He was not an eloquent lecturer, and his ideas were not always clearly expressed in his writings. He died before his work was finished, and his *magnum opus*, his museum, was left without an elucidating catalogue. Only two men remained who had an intimate knowledge of the museum and of the manuscript notes which revealed the mind of its originator—Everard Home and William Clift. All the authentic information contained in this book confirms the view of posterity that Everard Home acted in a manner calculated to raise his own reputation at the expense of that of his great teacher. It was to William Clift that we owe the original preservation and orderly arrangement of the Hunterian Museum and the salving of many of Hunter's original writings. If there had been no William Clift the greatness of Hunter would have been sadly dimmed if not eclipsed.

William Clift came as an uneducated lad of 17 to assist Hunter. He could write a neat and clear hand and had some facility in drawing, and, fortunately, he was a careful observer. He came to scientific work with no preconceived ideas, and his observations are to be trusted. Clift's mind was like a sensitive negative upon which shone the light of Hunter's intellect and character; though the exposure was for but a brief period the picture which developed in Clift's consciousness was clear and definite and guided his conduct throughout the remainder of his long life. To many the life of Clift is the best revelation of the greatness of his master.

Clift was said somewhat to resemble John Hunter, and it is related that when some person mentioned to him that this likeness was something more than a mere coincidence Clift replied: "If I thought what you insinuate were true, there is not a Duke in London I would touch my hat to." Whether this story be true or not, it certainly truly illustrates the spirit which guided the life of Clift.

It is rather strange that there has been no previous life of Clift, but this book makes amends for the delay, for it is well written and very well illustrated and is authoritative. It contains much interesting information about the early history of the Royal College of Surgeons and gives us fleeting glimpses of many celebrities of the past. We cordially recommend this readable volume to every good surgeon.

ZACHARY COPE.

NEUROPATHOLOGY

Fundamentals of Neuropathology. By William Brooks Dublin, M.D. (Pp. 685+xxiii; 329 figures. £6 13s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1954.

The upward trend in price and weight of textbooks is exemplified by this volume, which weighs over 4 lb. In substance it is a gallant endeavour to cover the common ground between the general pathologist, neuropathologist, neurologist, and psychiatrist. Since historically the neuropathologist has been more closely allied to the clinical specialists than to the general pathologists, the link with the latter has needed strengthening. This book should go a long way to promoting this, because at all points it relates the various pathological conditions of the nervous system to those of other organs and tissues, as well as outlining the principal clinical manifestations. It is also of help that the author has eliminated the germanistic jargon so beloved of neuropathologists, and has used terms that any pathologist can understand. It may be wondered, though, why "kernicterus" is preferred to "nuclear jaundice."

The style is curt and dogmatic; at times the bald statement provokes an answering query. It may be doubted, for example (p. 479), that approximately 1 in 10 meningiomas is malignant. Boeck's sarcoid is firmly labelled as "non-caseating tuberculosis" (p. 177), which may, as many think, be incorrect. There is then, at many points, the individualistic approach, but in general the text is sound and well balanced. The numerous illustrations, which include three colour plates, are mostly excellent. A bibliography of 496 references is appended, nearly all of them derived from North American sources; in many instances a more informative article could have been quoted from this side of the Atlantic.

D. S. RUSSELL.

DISEASE OF THE LIVER

Diseases of the Liver. By Mitchell A. Spellberg, M.D., F.A.C.P. (Pp. 646; 93 figures. $16.50.) New York: Grune and Stratton, Inc. 1954.

This new book on liver disease is written by a clinician with a wide experience of internal medicine who has, moreover, made significant contributions to the experimental study of such disease in laboratory animals. This dual aspect of the author's interests is clearly revealed in the text. Although the major emphasis is laid, as it should be in a book written for practising physicians, on clinical pictures and on differential diagnoses, more than adequate attention is devoted to the considerable recent advances in knowledge acquired in the experimental laboratory.

The arrangement of the material is novel, and the freshness of novelty is retained in remarkable fashion throughout the volume. The usual preliminary chapters on anatomy and physiology are dispensed with, but their subject matter is skilfully incorporated elsewhere. The chapter on laboratory tests of hepatic function with which the book begins discusses the underlying mechanisms so thoroughly that there is very little fundamental hepatic physiology omitted. The section dealing with the hepatic diseases resulting from disturbances in the major vessels gives the reader a picture of the liver's anatomy which has a dynamic quality usually lacking in the more academic anatomical descriptions. The emphasis on purely clinical aspects is especially shown in the chapter on differential diagnosis of jaundice, which occupies over 10% of the text, and throughout the book, wherever the classification of the various types of hepatic disease is being considered, it is the classification most useful clinically that is favoured and elaborated. The final chapter is devoted to the treatment of diffuse liver disease and liver failure. This gives in useful detail the widely accepted therapeutic regime for liver disease in general. Specific therapy for individual diseases is discussed with the disease in question. This avoids unnecessary repetition and greatly facilitates reference.

In short, it is an admirable book, eminently readable, and can be recommended without reservation.

L. E. GLYNN.

The Dorset Coastline (Longmans, Ltd., Dorchester, price 15s. net) is written with infectious enthusiasm by Dr. Llewellyn Pridham and illustrated with a magnificent series of photographs taken by Edwin Kestin. The author makes the bold claim that there are more interests in this stretch of shore—from Old Harry to the Cobb at Lyme Regis—"than in any other corresponding stretch of coastland the world over." Those brought up, as Dr. Pridham was, near the sea in Dorset will agree with him without hesitation: the names of the coves and cliffs—Dancing Ledge, Winspit, Worbarrow, Arish Mell, Durdle Door, White Nose, Golden Cap—are enough to evoke the lonely beauty of the Wessex shore. Turning over the pages of this book might even shake the faith of those who are firmly convinced of the superiority of some other county's coastline. Dr. Pridham has not attempted to write a guide book, but picks out for comment, "from a personal and photographic point of view," the scenes and activities which attract him most. Sailing is one of his loves, and, a good Navy man, he has a soft spot for a rough place, the Isle of Portland. Another Llewellyn and Dorset essayist, Llewellyn Powys, would have approved of this book.

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DORMANCY IN CANCER

The progressive course of most clinical cancer has led to the assumption that the growth of malignant tumours is usually continuous and uninterrupted from beginning to end. Though this may be the general rule, there are certainly many exceptions, as is well known to all who have watched the course of the disease in either treated or untreated patients. Exceptional cases are often of exceptional interest, and that is certainly true of those rare cases in which cancer seems to have remained in a latent condition for many years. Hitherto the word "latent" has been generally used to describe this phenomenon, but Professor Geoffrey Hadfield, in the Kettle Memorial Lecture which we publish in our opening pages this week, has chosen the more expressive word "dormant" to describe "malignant cells which, although remaining alive in the tissues for relatively long periods, show no evidence of multiplication during this time, yet retain all their former and vigorous capacity to multiply." Is the use of the word "dormant" justified in the present state of our knowledge? "Latent" is non-committal: it implies only the concealment or absence of a tumour's clinical manifestation. Dormancy, on the other hand, is apt to suggest a resting phase, or, more fancifully, almost as though the cancer cells were in some kind of sleep. Professor Hadfield's object, however, is to recall the long-attested phenomenon of latency in human cancer and then to describe some interesting new experiments recently carried out by Dr. James Craigie. These prove that cancer cells in some animal tumours may survive for long periods when frozen solid and stored at low temperatures such as −70° C. The astonishing capacity of survival of tumour cells at very low temperature has been known for many years, and a closer study of this remarkable phenomenon has shown that the survival rate of frozen tumour cells is higher if the tumour is frozen slowly. This is explained on the supposition that slow freezing enables tumour cells to effect certain physico-chemical and structural adjustments which seem to be essential if they are to resist anoxia and dehydration. Investigating this phenomenon, Craigie found that when tumour tissue had been maintained at −70° C. for many months and was rapidly thawed and then quickly examined he could recognize a variable number of small, highly refractile cells which had a higher capacity than others to resist and survive anoxia, dehydration, and metabolic arrest. He has named these more resistant cells "paramorphic," and he asserts that the tumour-inducing activity of a thawed-out malignant tumour after a long period of anoxia is directly related to the number of paramorphic cells present in it.

These experiments on the dehydration and freezing of transplantable tumour tissue suggest that a case can be made out for the existence in such material of particular cells with exceptional powers of resistance which, during adverse conditions, remain in what may be called a "dormant" state. Whether or not Craigie's paramorphic cells occur in normal tissue, or in human tumours, still remains to be proved, and further information on these points will certainly be awaited with interest. Until this has been established, it does not seem likely that any close comparison can be made between the first phenomenon to which Professor Hadfield drew attention—namely, the arrested growth of a human tumour—and the survival of cancer cells in animal tumour tissue frozen at −70° C. None the less, the closer study of paramorphic cells of transplantable animal cancer may eventually throw some light on the obscure problem of the biological state of apparently dormant cells which persist in human tumours. As Professor Hadfield says, "The fact that malignant cells can be induced to survive long periods of experimental metabolic arrest would appear to offer an explanation of their *in vivo* ability to withstand separation from their parent growth until a capillary circulation is provided for them." He suggests that this may apply to microscopic foci of isolated cells which form the nucleus of a metastasis, or to groups of cells of comparable size which become completely detached from their parent growth during the process of malignant infiltration.

ANTIBIOTICS AND GROWTH

Medical interest in antibiotics has been largely confined to their bacteriostatic and bactericidal effects. Yet, in contrast to these, low concentrations of antibiotics have been shown to stimulate the growth of bacteria, yeasts, and protozoa,[1] and certain virus tumours.[2 3] The use of antibiotics to enhance the

growth of higher plants and of animals is still in the experimental stage. Terramycin in a concentration of 1 to 5 parts per million of soil stimulated the germination of narrow-leaved sorrel seeds and increased their growth rate and the net weight of the seedling above ground.[3] Diamine and procaine-penicillin stimulated the growth of radish seedlings, and the addition of terramycin to gelatin coating of seeds reversed the inhibition of germination caused by gelatin coating alone.[3] In 1946 Moore *et al.*[4] found that streptomycin increased the growth rate of chicks on a purified diet, but the practical application of this aspect of the action of antibiotics to animal husbandry was not established until fours years later. Stokstad and Jukes[5 6] then found that the addition of aureomycin to normal feeds enhanced the growth of chicks, turkeys, and pigs. Aureomycin, streptomycin, terramycin, and penicillin increased the growth rate of calves[7] and goslings,[8] but were without effect on ducks.[9] Evidence of a growth response to antibiotics in lambs is conflicting.[7] Among laboratory animals the growth of rats was stimulated by aureomycin, terramycin, streptomycin, and penicillin[10] and that of mice by aureomycin.[11]

The mode of action of antibiotics in stimulating growth is not yet fully understood. In treated animals the acceleration of growth is often accompanied by increased efficiency in utilization of food. It is not clear whether antibiotics act by improving food utilization or by increasing growth rate directly, in which case food utilization would improve because a smaller proportion of the total food intake is needed for maintenance in a fast-growing animal.[12] There is evidence of a sparing action on the vitamin-B complex in plants[3] and animals.[13–15] But it is not clear whether this is by enhancement of bacterial synthesis of essential growth factors or by inhibition of the growth of bacteria which compete with the host for these factors. Another possible action is by inhibiting the growth of bacteria which produce toxic substances inimical to the growth of the host, which receives some support from the work of Coates *et al.*,[16] who showed that antibiotics have little or no effect on the growth of chicks kept in an environment where poultry have not previously been housed. Stokstad[17] also noted that the best response in pigs occurred when they had had diarrhoea prior to antibiotic treatment. Although antibiotics have no effect on the growth of the chick embryo[17] they have been shown to alter the normal process of mitosis in the onion-root,[18 19] and the growth rate of implanted carcinomata increased in rats fed with small amounts of aureomycin.[20]

There is little information about the effects of antibiotics on the growth of humans. Robinson[21] reported that, when 50 mg. per kg. body weight of aureomycin was given to one of premature twins or triplets—the other twin or triplets acting as controls—the aureomycin-treated infants showed an average daily gain in weight of 29.5 g. compared with 18 g. in the control group. None of the thirteen aureomycin-treated infants died, while five of the fifteen controls did. However, these results may have been due to loading of the control group with the weaker infants, many of whom had been assigned originally to the test group but were found to be unable to tolerate aureomycin. Robinson concluded that aureomycin acted by preventing infection rather than as a growth factor. Other workers have considered the effect of aureomycin on the nitrogen balances of undernourished adult man.[22] The urinary nitrogen and riboflavin excretions increased during the period of treatment. It would have been surprising if there had been a beneficial effect on the nutritional state in adults, since the reports on animals and plants suggest that antibiotics exert their maximum effect during the period of active growth.

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[11] Vijayaraghavan, P. K., *et al.*, ibid., 1952, **36**, 127.
[12] Braude, R., *et al.*, *Nutr. Abstr. Rev.*, 1953, **23**, 473.
[13] Stokstad, E. L. R., and Jukes, T. H., *Proc. Soc. exp. Biol. (N.Y.)*, 1951, **76**, 73.
[14] Biely, J., and March, B., *Science*, 1951, **114**, 330.
[15] Coates, M. E., *et al.*, *Biochem. J.*, 1951, **49**, lxviii.
[16] *Nature, Lond.*, 1951, **168**, 332.
[17] *Antibiot. & Chemother.*, 1953, **3**, 434.
[18] Wilson, G. B., *J. Hered.*, 1950, **41**, 227.
[19] —— and Bowen, C. C., ibid., 1951, **42**, 251.
[20] Sokoloff, B., and Eddy, W. H., *Cancer Res.*, 1951, **11**, 282.
[21] *Lancet*, 1952, **1**, 52.
[22] Gabuzda, G. J., *et al.*, *J. clin. Invest.*, 1952, **31**, 631.

RADIOLOGICAL EXAMINATION OF THE BILE PASSAGES

Most surgeons interested in the biliary tract feel the need for some reliable aid from the radiologist when confronted with a complicated diagnostic problem. The extent and accuracy of the information obtainable by *x*-ray examination of the gall-bladder and bile passages are very variable, yet certain recent developments have lately brought the whole subject under scrutiny, and a review of the present position may be helpful. Plain radiography is of limited value, but occasionally does more than merely demonstrate radio-opaque calculi, for gas in the biliary tree is sometimes seen, or barium after a barium meal—

proof of an abnormal fistula between the gastro-intestinal and biliary systems or incontinence of the sphincter of Oddi. An interesting review of this finding has recently appeared in the *British Journal of Radiology*.[1] Barium studies of the upper gastro-intestinal tract play only a small part in the study of biliary problems, but may sometimes demonstrate that obstructive jaundice is due to a pancreatic or ampullary neoplasm.

Direct contrast radiography depends upon the introduction of a radio-opaque dye into the biliary apparatus. It may be achieved by oral and intravenous cholecystography and cholangiography, by operative cholangiography, or by percutaneous transhepatic cholangiography. The original compounds used for oral cholecystography and cholangiography contained a relatively low iodine content and were not excreted in the liver bile in sufficient concentration to throw a shadow. The only part of the biliary system to be visualized was a normally concentrating gall-bladder and, very occasionally, the common bile duct if a film taken directly after the fatty meal coincided with the actual emptying of the gall-bladder. The newer compounds, such as "telepaque" and "teridax," throw a denser shadow in the gall-bladder, and serial films taken during the phase of gall-bladder contraction after a fatty meal allow the cystic and common bile ducts to be visualized in a high percentage of cases. Occasionally the extrahepatic bile passages of a patient whose gall-bladder has been removed may be demonstrated by oral cholangiography with these substances, but the information obtained is seldom entirely reliable.

Recently a compound has been developed for intravenous administration capable of outlining the extrahepatic biliary apparatus even after the gall-bladder has been removed. First described in 1953 by Frommhold,[2] most of the earlier work was done in Germany, where the compound is called "biligraffin." An American preparation, "cholograffin," is chemically identical. This compound may have toxic effects, and it is recommended that a test dose of 1 ml. should be given intravenously before injecting slowly the full 40–60 ml. needed for the examination. Excretion of radio-opaque bile is apparent after ten minutes or so, the hepatic ducts becoming visible first. The gall-bladder, if present, is visible after 30 to 60 minutes, maximally after 2 to 2½ hours. The advantages of this preparation are obvious, but it has its limitations. In the presence of parenchymatous damage, the liver fails to take it up, and excretion by the kidneys occurs instead. Similarly an obstructed biliary system, full of viscid bile, allows only slow diffusion into it of the dye, even if the liver cells can excrete it. Thus intravenous cholangiography of the jaundiced patient is seldom satisfactory and may possibly carry some risk.

Operative cholangiography—which is well described by Mr. E. S. R. Hughes and Mr. R. H. Kernutt elsewhere in this issue—may be carried out with a needle or catheter inserted into the unopened common bile duct at the start of an operation, or may follow exploration of the duct as a safety measure before the abdomen is closed. The latter is undoubtedly a wise precaution in many cases of cholelithiasis, but opinions differ on the value of injecting dye into the unopened duct. Some surgeons, notably McNeill Love[3] in this country, place great reliance upon this preliminary cholangiography and believe that a film showing no abnormality can exclude calculi with sufficient certainty to make it unnecessary to open the duct. Others, such as Maingot, have stressed the difficulties in interpretation and in particular the dangers of relying upon negative films. Neither opinion should be lightly rejected, but at the moment the view seems to be gaining ground that cases sufficiently doubtful to warrant operative cholangiography require exploration of the duct.

Percutaneous transhepatic cholangiography is a term used to describe a method of injecting a radio-opaque dye directly into a dilated intrahepatic bile duct in cases of obstructive jaundice.[4 5] Performed under local anaesthesia, the technique is not difficult, and good, clear films can be obtained. Unfortunately the pressure in the obstructed bile passages is high, and there is a very real risk of puncture being followed by leakage of bile into the peritoneal cavity. It is true that this accident need not greatly endanger life if the abdomen is opened at once, but it is hardly desirable to start an operation upon the biliary tract with a shocked patient and the tissues sodden with bile. At present it appears that the risks of this investigation outweigh the probable advantages. A possible exception might be made in a case of post-traumatic stricture of the common bile duct, but even here, if transhepatic cholangiography is indicated, it should be performed either at operation or immediately before it.

To sum up, results with oral cholecystography and cholangiography have improved, and intravenous cholangiography has provided a useful new method of investigating the unjaundiced patient. Operative cholangiography is particularly helpful as a final check, after exploration of the common bile duct for

[1] Scott, M. G., Pygott, F., and Murphy, L., *Brit. J. Radiol.*, 1954, **27**, 253.
[2] *Fortschr. Röntgenstr.*, 1953, **79**, 283.
[3] *Brit. J. Surg.*, 1952, **40**, 214.
[4] Nurick, A. W., Patey, D. H., and Whiteside, C. G., ibid., 1953, **41**, 27.
[5] Smith, Rodney, *Progress in Clinical Surgery*, 1954, London.

stones, before closing the abdomen, and is preferable to post-operative cholangiography performed a week after operation before removing the T-tube. No safe, effective method of *x*-raying the biliary tract of a jaundiced patient has yet been developed, and non-operative puncture of obstructed bile passages is only exceptionally justified.

CANCER CELLS IN DIAGNOSIS OF POLIOMYELITIS

The pioneer work of Enders and his colleagues[1] on the application of tissue culture methods to the study of poliomyelitis has been the outstanding development in poliomyelitis research in recent years, for it has enabled a wide range of problems to be studied hitherto restricted by elaborate and costly animal experiments. The original observations made on simple cell cultures of human embryonic tissue showed that virus multiplication occurred in both nervous and non-nervous tissues. Later it was found that both adult human (normal and malignant) and monkey tissues supported the growth of all three strains of poliomyelitis virus in tissue culture.[2] Many of the technical difficulties encountered earlier on have now been mastered and much progress has been made towards simplification and standardization of methods for use on a wider scale.

One of the difficulties that laboratories may be up against, certainly in Britain, will be the availability of suitable tissue for culture. So far only human and monkey tissues have been found capable of supporting virus growth, and unless a continuous supply of the same tissue can be ensured it is difficult to obtain consistent results which can at the same time be compared with the findings of other workers. A recent report by Syverton, Scherer, and Elwood[3] on the use of a strain of human carcinoma cells in the diagnosis of poliomyelitis suggests that some of these difficulties may be overcome. The "HeLa" strain of epithelial cells, as it is called after the name of the patient, was isolated three years ago by Gey and his associates[4] from a carcinoma of the cervix and has since been maintained by serial transfer. These cells grow profusely in sheets on glass surfaces in the absence of plasma, and in a preliminary report Syverton and Scherer[5] showed that all three strains of poliomyelitis would multiply in these cells, producing characteristic cytopathogenic effects after one to three days. In the past eighteen months over 300 strains of poliomyelitis virus have been isolated and typed by this technique, as well as a number of other viruses. This in itself is good evidence of the practicability of the method, but what is more important than the ease of handling these cultures is the fact that they are relatively stable, can readily be produced in bulk, and will provide a standardized method by which some comparison of results can be obtained.

[1] *Science*, 1949, **109**, 85.
[2] Weller, T. H., *New Engl. J. Med.*, 1953, **249**, 186.
[3] *J. Lab. clin. Med.*, 1954, **43**, 286.
[4] *Cancer Res.*, 1952, **12**, 264.
[5] *Fed. Proc.*, 1953, **12**, 462.

Now that tissue culture has been put on a practical footing there are many new aspects of poliomyelitis research which can be investigated. Apart from providing a laboratory method of diagnosis, either by isolation or by antibody estimation, tissue culture may be of even greater value in epidemiological surveys and in assessing the antibody response to poliomyelitis vaccines. Clearly virus grown on cancer cells will not be suitable for vaccine production, but it is of some note that the cell descendants of this malignant tumour can now be put to good use towards eventual control of poliomyelitis.

FLUORIDATION IN BRITAIN

Four places in the British Isles—Watford, Darlington, Anglesey, and Kilmarnock—have recently accepted an invitation to add fluorides to the public water supply, and the necessary apparatus is being ordered from the United States. Within twelve months these four schemes should be under way. They are being undertaken in accordance with the recommendations of the United Kingdom mission which visited North America in 1952. It evaluated the evidence, to which more has since been added, showing that dental caries is much less prevalent in people who throughout their lives drink water with a natural fluorine content of 1 p.p.m. or more than in those whose water supply is practically free of fluorine. Surveys providing confirmatory evidence of this have been made in many parts of the world—in North America by Trendley Dean,[1] in South Africa by Ockerse,[2] in India by Venkateswarlu *et al.*,[3] and in England by Weaver,[4] Forrest and Parfitt,[5] Cowan,[6] and Chalmers Clarke.[7] In five large-scale experiments conducted in North America since 1945 fluoride has been added to the public water supply as a prophylactic against dental caries, and a reduction has occurred in the incidence of dental caries in the younger children to the level of those drinking water with a naturally occurring fluoride content. One thousand communities in the United States are already adding fluoride to their drinking-water. Even so, it should not be assumed that the same results will be obtained in Britain as in the United States, for habits, diet, climate, and dental caries experience differ, but a reduction in dental caries to the level of those living in high-fluorine areas in this country might reasonably be expected.

Fluorine is present in almost all food substances from 0.2 p.p.m. to 20.0 p.p.m. or more, but it is most readily absorbed from drinking-water. The benefit derived from taking water containing fluorine is almost entirely confined to the period of calcification of the teeth, from birth to the age of 6 or 8 years, but the increased resistance to dental caries so obtained remains throughout life. Children vary in their daily habits. Some drink a great deal of water, others very little, and foods containing more or less fluorine are shunned or accepted

[1] American Association for the Advancement of Science, *Dental Caries and Fluorine*, 1946, 5–31.
[2] *Department of Health Issue*, 1947, South Africa.
[3] *Indian J. med. Res.*, 1952, **40**, 4.
[4] *Proc. roy. Soc. Med.*, 1948, **41**, 284.
[5] *Monthly Bull. Minist. Hlth (Lond.)*, 1951, **10**, 104.
[6] *Med. Offr*, 1952, **88**, 25.
[7] Ibid., 1954, **92**, 4.
[8] The Fluoridation of Domestic Water Supplies in North America as a means of controlling Dental Caries, 1953, H.M.S.O., London.

variously. The amount of fluorine ingested by an individual cannot readily be assessed, nor the amount absorbed estimated; but, by urine analysis, excretion and hence absorption can be measured. By such medical and dental findings the suitable level of fluorine content of drinking-water for this country will be found.

The possible hazards of continuously ingesting fluoridated water to the level of 1 p.p.m. have been carefully studied, and this study is being continued in America by the Institute of Dental Research, the National Institute of Health, and the Public Health Service. Moreover, it was one of the terms of reference of the United Kingdom Mission,[5] which reported: "There is no scientific evidence that there is any danger to health from the continued consumption of water containing fluoride in low concentrations." Many public health measures have met with a certain amount of opposition. This safe, unobtrusive, and beneficial measure is no exception. Where it has been proposed or introduced, some individuals find it necessary to resist the element of "compulsion" entailed; other genuinely believe that their bodily discomforts are caused by drinking the fluoridated water, and may seek the advice of their family doctor. In one community such complaints were received before fluoridation had begun and in another after it had been discontinued.

FAMILY SERVICE UNITS

In 1940 a small group of people on Merseyside organized themselves into a unit and began to give social service for bombed-out families in shelters and rest centres. They soon found that their time was largely occupied with those families with little personal, spiritual, or material resources, the sort of family which even in peacetime is unable to fend for itself, pay its way, or conform to law and custom. These families constitute a stratum of society which has been recognized at least since Charles Booth[1] described them as "the submerged tenth." Later they were referred to as the "social problem group"[2]: to-day we call them problem families. In the Wood Report[3] of 1929 it had been noted that mental backwardness was often to be found in this type of family and that the same families contained a high proportion of "insane persons, epileptics, paupers, criminals, unemployables, habitual slum dwellers, prostitutes, inebriates, and other social inefficients." Family Service Units, the national organization which took over and developed the work of the Merseyside and other units in 1947, deals with similar problems to-day. The methods used by F.S.U. case workers are simple to understand though less easy to operate. They are based on the case worker's friendship with the families concerned and practical help to overcome the difficulties which have defeated them. Families are usually referred to the units by other statutory or voluntary agencies such as health visitors or the local Council of Social Service, and the treatment at first is intensive, often entailing a daily visit for weeks or months. It is the practice not to give financial help, though occasionally the case worker may have to purchase a bucket, scrubbing-brush, and soap, and go armed with these in order to tackle, with the mother, the arrears of laundry and cleaning. The most elementary equipment is frequently missing from these homes. Often the gas or electricity has been cut off because of non-payment of accounts. The case worker will then try to persuade the tenant to agree to the repayment of the debt by weekly instalments, and, reinforced with the first instalment and the promise of more to come, may then succeed in arranging with the authority for the gas or electricity supply to be reconnected. Children who have been playing truant may have to be taken to school by the case worker for some weeks to re-establish the habit of regular attendance. Employers, medical officers of health, housing managers, solicitors, and many others must be interviewed on behalf of the family in trouble in the struggle towards social rehabilitation.

The fifth annual report[4] of Family Service Units records that there are now ten units in operation, two in London (another has since been added) and eight in the provinces—Liverpool, Manchester with Salford and Oldham, Sheffield, Leicester, Birmingham, York, Bristol, and Bradford. The case workers are usually young men and women with a strong sense of vocation and willing to do an arduous and often disheartening job for a very modest salary. Most of the candidates have had some training in social science, and the units are used by university social science departments to give practical instruction to their students. Financial support has come mainly from individual subscriptions, from trusts, and from local authority grants. The Bristol and Bradford units are in fact wholly maintained at local authority expense. It has been estimated that the cost of some of these families to the State and local authorities may reach £1,000 per annum: to maintain one child for a week in a children's home may cost up to £5; in an approved school, over £6; in a residential nursery £8. In the words of the annual report:

> "In these circumstances, if a unit worker devoted all his attention to only one or two families and by doing so made no permanent impact but merely prevented the removal of the children, that worker would be saving a good deal more than his salary."

It is very difficult to estimate success in this sort of work. A good many families seem quite incorrigible, in others only partial success is obtained. One typical provincial unit which has dealt with 69 families over a period of four years has discharged 32 families, but the remainder are still in need of help. Of the discharged families, 14 were regarded as no longer problems to the community, in 4 more good progress had been made though certain problems remained intractable. Three families had refused further help, and 11 families had been transferred to other agencies because they were considered unsuitable for the kind of help Family Service Units can give or to avoid overlapping.

Although Family Service Units have achieved some remarkable successes with problem families where all other agencies have failed, the cure of this social disease is often impossible, and until the

[1] *Life and Labour of the People of London*, 1889, London.
[2] Blacker, C. P., *A Social Problem Group*, 1937, London.
[3] *Report of the Mental Deficiency Committee*, 1929, H.M.S.O., London.
[4] *Family Service Units: Fifth Annual Report*, 159, Westbourne Grove, London, W.11.

causes of family failure are better understood prevention cannot begin to operate. For this reason a whole-time research worker has been appointed with funds made available by the Carnegie United Kingdom Trust to investigate this complex problem.

GALACTOSAEMIA

Galactosaemia is the name given to a serious inborn error of metabolism, probably due to inheritance of a recessive gene, which is evident in early infancy. The condition may well be commoner than the small number of recorded cases suggests, and two papers on it appear in our columns this week—by Drs. P. J. N. Cox and R. J. P. Pugh at p. 613 and Drs. M. W. Arthurton and B. W. Meade at p. 618. The clinical picture is characteristic. The infant appears normal at birth, but soon fails to thrive, becomes irritable, and refuses or vomits feeds. Jaundice commonly follows, and the liver and spleen are found to be enlarged. The child becomes increasingly wasted, and a liability to infections and haemorrhage may confuse the diagnosis. Examination of the urine reveals albuminuria, casts, bile pigments, and a substance which reduces Benedict's solution. Death is common at this stage; but, if the infant survives, cataracts and mental retardation are inevitable. Chemical tests show that the reducing substance in the urine is galactose, but they are tedious and not always reliable; paper chromatography[1] is the best way of confirming the diagnosis. The galactose tolerance test is grossly abnormal and it may sometimes aggravate symptoms.[2] In spite of clinical evidence of liver damage, liver function tests are often normal; some cases show a severe amino-aciduria. Early treatment results in dramatic improvement, and consists in giving a lactose-free diet, the basis of which is a protein supplement, to which is added sucrose, fat, vitamins, iron, sodium, and potassium. Special lactose-free feeds have been recommended, but may not be generally available.

It is clear that the infant with galactosaemia cannot assimilate the lactose present in human or artificial milk. This is normally broken down to glucose and galactose, and the latter is metabolized by specific enzymes in the liver to form glucose-1-phosphate, which is then built up into glycogen. It is probable that this enzyme system is deficient in galactosaemia, and that the large amounts of galactose exert a toxic effect on the liver. Post-mortem changes are confined to this organ, which shows a severe necrosis, with typical alveolar arrangement of liver cells, fatty infiltration, and diffuse fibrosis. It would be interesting to know whether the amino-aciduria is the result of this damage or is due to an innate tubular defect as in the Fanconi group of syndromes.[3] Cataracts probably result from a direct action of galactose on the lens, as they have been produced in young animals fed this substance.[3] Galactose is a constituent of the cerebrosides of nervous tissue, and cerebral damage is presumably related to abnormal galactose metabolism in the brain. While much remains to be learnt about galactosaemia, one fact is clear. The difficulty of obtaining a specimen of urine in the young infant is little excuse for failure to diagnose a disease where prompt treatment may prevent death or severe disablement.

[1] Bickel, H., and Hickmans, E. M., *Arch. Dis. Childh.*, 1952, **27**, 348.
[2] Jackson, W. P. U., and Linder, G. C., *Quart. J. Med.*, 1953, **22**, 133.
[3] Mitchell, H. S., and Dodge, W. M., *J. Nutr.*, 1935, **9**, 37.

MIDWIVES INTERNATIONAL CONGRESS

All this week some 700 midwives from 46 different countries have been assembled in London for the Congress of the International Confederation of Midwives. The Royal College of Midwives, under its president, Miss N. B. Deane, has been responsible for the arrangements. For over 50 years, except during periods of war, European midwives have been meeting from time to time in one or another country and have pooled experiences and discussed professional problems. It was in Prague, in 1925, that some procedural rules were agreed upon for a permanent international organization, and out of this the International Midwives Union, with its own secretariat and central office, came into being. This body amply justified its existence until the war extinguished its life. But its spirit survived, and in 1949 at a meeting in London the threads were gathered up and the International Federation of Midwives Organization was formed. This replaced, but was based upon, the old International Midwives Union, with the hope that the new organization, from being mainly European, would be truly world-wide. The present conference would seem to have fulfilled the hopes of the founders of the International Confederation. Twenty-eight countries which have their own midwives' organizations have sent official delegates and others have sent observers. Many other midwives have travelled long distances of their own accord. Those from India, Japan, Hong Kong, and Formosa have mingled with those from the West. The only countries which refused the invitations sent to them were the Soviet Union and Czechoslovakia. It is pleasing to record that British midwives, of whom about 400 are attending the conference, have subscribed between them over £4,000 to a hospitality fund.

The congress was opened on September 6 by the Minister of Health, Mr. Iain Macleod, who referred to some of the advantages of childbirth in the home. Professor Nicholson J. Eastman, of the Johns Hopkins University School of Medicine, Baltimore, gave an inaugural address on "The Midwife and World Health." The discussions during the week have been on such subjects as the professional responsibilities of the midwife, the midwife's part in reducing maternal deaths, and the midwife's training. It is interesting that Dr. R. J. Minnitt, who demonstrated his gas-and-air apparatus to the conference in London in 1934, was again speaking this year about relief of pain in childbirth. There can be no doubt that all those at this week's conference will have been refreshed by interchanges of views and experiences, and it is to be hoped that much will have been done to strengthen international collaboration among midwives with all the manifold benefits which such collaboration cannot fail to bring.

A memorial service to the late Dr. Alfred Cox, medical secretary of the British Medical Association from 1912 to 1932, will be held at St. Pancras Church on Thursday, September 16, at 12 noon.

BRITISH ASSOCIATION

[BY A SPECIAL CORRESPONDENT]

The 116th annual meeting of the British Association was held at Oxford from September 1 to 8 under the presidency of Dr. E. D. ADRIAN, F.R.S., whose address was reported in last week's *Journal* (p. 587). There were, as usual, a number of contributions which directly or otherwise were related to medicine.

Control of Cell Division

A new approach to the control of cell division in living organisms was described in the Section of Zoology by Professor M. M. SWANN (Edinburgh University), the factors concerned in the general problem being taken to include the availability of energy, the stage of growth of the cell, effects loosely described as "contact" with other cells, differentiation, and carcinogens. He had selected the energy factor as the one best suited to an initial investigation by simple experiments. The eggs of sea urchins were exposed to carbon monoxide (as a means of temporarily shutting off energy) during different periods of time, and a delay in division resulted which was equal to the duration of exposure. Division, if already begun, was completed, and the next division was then delayed by the same amount. It seemed probable that the energy-storing substance was a complex phosphate; and the equality between exposure time and delay (in whichever division) suggested that the substance concerned served no other function in cellular metabolism. A search for such a phosphate, of which the quantity present varied according to whether cell division was approaching or had lately been initiated, was carried out recently at the Millport Station of the Scottish Marine Biological Association, using paper-chromatographic separation, but the results were not available in time for the meeting.

Obesity

A discussion on obesity was held by the Section of Physiology. Dr. J. M. TANNER (St. Thomas's Hospital Medical School) argued that it was necessary to distinguish not merely between "overweight" and "overfat" but also between the overall quantity of fat in an individual and fat content per fat cell. He suggested the term *lipoplethory*, following Lawrence,[1] to designate the relative fullness of cells with fat. The view could then be taken that a person of any build might become, *a priori*, lipoplethoric, but that only those relatively high in endomorphy (Sheldon) could produce a sufficiently high percentage of body fat to be called obese. Serum cholesterol concentration, which was related but not very closely to body fat, might be more closely related to lipoplethory. Although the percentage of weight carried as fat was what mattered in therapeutic medicine, a guide to the number of fat cells possessed by an individual might well be valuable in preventive medicine. In well-nourished countries, persons with many fat cells were the ones who needed to diet.

Dr. A. P. MEIKLEJOHN (Edinburgh University) pointed out that there was much more to be learnt about the reactions of the body to overfeeding and their relation, direct or indirect, to arterial degeneration. Pending the results of fundamental research, he commended a look at the patient or the weighing balance as the best guides. But he criticized the use in Great Britain of American tables which still seemed to be based on the average heights and weights of Americans seeking life assurance in 1885–90—though with recent theoretical adjustments (1942–3). He suggested that the British Association, which organized and carried out the first thorough anthropomorphic survey in Great Britain (published in 1883), might undertake a further survey, and that this could be usefully integrated with a study of the complications of obesity. Here was a fine field for research workers in gerontology, possibly assisted by the new College of General Practitioners, and advised by the Committee on Growth and Form of the Medical Research Council. Professor JEAN MAYER (Harvard University) described an experiment in which a "waltzing" mouse was mated with a genetically obese mouse, the result being a waltzing obese mouse, which, however, put on only one-sixth of the weight of one that was merely obese. In another experiment, an obese mouse, given an hour's work a day on a treadmill, was found to halve his weight gain, whereas more work, resulting in greater appetite, led to an increase in weight. He concluded that, for weight reduction, one should take exercise, but not too much.

[1] *British Medical Journal*, 1951, 1, 373.

Genetics and Medicine

During an all-day session on genetics, held jointly by the Sections of Zoology and Botany, Professor L. S. PENROSE, F.R.S. (University College, London), questioned the soundness of eugenic arguments to the effect that, behind a façade of improvement due to hygienic and nutritional conditions, the population was deteriorating physically and mentally because of the preservation of hereditary weaklings. Genes that were unfavourable in one context were often favourable in another; for example, the sickle-cell gene protected its possessor from malaria, and control of malaria reduced its incidence. In other cases, disease resulted from an exceptional concatenation of abnormal genes. It was thus unsound to try to get rid of particular genes, unless the harm done by them was known to outweigh the good, and genetic variety was, on general principles, an advantage. Knowledge of inherited biochemical constitution, based on genetics, would, however, help directly in the attack on disease, and knowledge of the genetics of pathogenic parasites was indirectly useful. The latter aspect was taken up by Dr. G. PONTECORVO and Dr. J. A. ROPER (Glasgow University), who described the analysis of novel (parasexual) systems of recombination in micro-organisms, and discussed the significance of such findings for host-pathogen relationships.

"Healthy" Hallucinations

In the Section of Psychology Mr. J. C. RAVEN (The Crichton Royal, Dumfries) quoted examples of hallucinations which, unless rejected as carefully planned misrepresentations, made it impossible in his view to go on dismissing hallucinatory experiences as merely "morbid imaginations" or "distortions of fact." If recorded hallucinations were arranged in order from those most obviously morbid to those most obviously healthy, characteristic similarities and differences were found between them. Hallucinations, in general, arose during tension or when a personal problem required solution; but, whereas in mental illness they tended to take the form of fixed, fragmented, or encapsuled ideas beyond the patient's control or understanding and often seemed detrimental, those experienced during times of well-being tended to be mobile and appropriate. They appeared to be intimately related to past and present events and to increase awareness of their significance, and were also related to the conduct of other people. They expressed a sympathetic responsiveness, and the percipient was usually aware of the part that they played in apprehending and interpreting what was experienced. Only as recognition was given to the subjective nature of experience and to personality as something essentially experienced in human relationships was it likely that the context of hallucinations would be understood, or any satisfactory concept of mind be formed.

Tropical Medicine

Recent investigations of the natural history of loaiasis, a disease which results from infection with a filarial parasite (*Loa loa*) and causes much suffering among the indigenous and European populations in certain parts of Africa, were described by Professor R. M. GORDON and Dr. W. E. KERSHAW (Liverpool School of Tropical Medicine). The work had been based on the Kumba laboratory in the British Cameroons. Prior to the establishment of the laboratory, it was known that loaiasis was transmitted from man to man by certain biting flies of the genus *Chrysops*, and that these flies were most numerous in the cleared areas surrounding small villages situated in the tropical rain-forest. The flies

had now been found to extend far beyond the cleared areas, and by the use of observation platforms, built to a height of 80 to 120 ft. above the forest canopy, information had been collected which suggested that loaiasis was not not confined to the human population but occurred also in the monkey population living in the forest, which thus formed a reservoir of infection.

MENTAL HEALTH AND PUBLIC AFFAIRS

INTERNATIONAL CONGRESS IN TORONTO

[BY A SPECIAL CORRESPONDENT]

The fifth International Congress on Mental Health was held in Toronto last month, under the auspices of the World Federation for Mental Health. The sponsoring host organizations were the Canadian Mental Health Association and the Canadian Psychological Association. The Congress began on August 14 and ended on August 21.

About 2,000 members attended, representing almost every discipline concerned with human relations and coming from some 50 countries. There was a large contingent from Britain, which included Dr. Walter Maclay, from the Board of Control, Dr. A. F. Alford, from the Ministry of Education, Dr. J. R. Rees and Dr. Kenneth Soddy, Medical Director and Assistant Medical Director respectively of the World Federation for Mental Health, and Dr. Doris Odlum, President of the European League for Mental Hygiene, who was also the official delegate of the British Medical Association.

The proceedings were divided into plenary sessions, technical sessions, and round-table discussions. Prior to the Congress itself three research symposia were held, dealing with problems of partnership in mental and public health, under the titles "Mental Health and Child Development," "Industrial Mental Health and Human Relations," and "Alcoholism." These paved the way for the main theme of the Congress, which was "Mental Health and Public Affairs."

The Plenary Sessions

After a warm welcome had been given to all the delegates by the Congress President, Dr. SIDNEY SMITH, of Toronto, the Minister of National Health and Welfare of Canada, Mr. PAUL MARTIN, addressed the inaugural meeting on "The Challenge to Mental Health in the World To-day." In Canada mental health was a problem of the first magnitude, he said. There were more than 65,000 patients in Canadian mental hospitals, and mental illness accounted for more lost working time than tuberculosis, cancer, and poliomyelitis combined. Prejudice and ignorance about mental diseases still constituted a formidable barrier to progress. Since a national mental programme had been instituted in 1948 more than 10,000 new beds had been provided in mental institutions and there had been a rapid increase in the number of mental clinics and mental health staffs. Federal expenditure on medical research now amounted to more than $500,000 annually, and more than $30,000,000 had been provided for all work in the field of mental health since 1948. There had been what appeared to be an increase in mental illness throughout the world during the past two decades, but that might well be largely owing to improved diagnosis and greater public understanding of emotional disorders.

The first plenary session was on mental health and spiritual values. The speakers were Sir GEOFFREY VICKERS, V.C. (London), and Dr. LEONARD W. BROCKINGTON (Toronto). Sir Geoffrey Vickers discussed the various philosophies which man had evolved from the earliest times, and said that it was obvious that all human beings fundamentally felt the need for some spiritual value. In order that life should be tolerable, it must hold some meaning and purpose beyond the purely material. This was the only enduring incentive and the only ideal through which man could attain to true mental health.

During the next five days a number of important papers were given in plenary session. Professor H. C. RÜMKE (Holland), President of the World Federation for Mental Health, spoke of "The Solved and Unsolved Problems in Mental Health." Professor W. MALAMUD (Boston) dealt with "Research in Relation to Schizophrenia." Dr. RONALD HARGREAVES, Chief of the Mental Health Section of the World Health Organization, discussed mental health in relation to public health. He pointed out that, once the medical profession had discovered something of the aetiology and nature of a disease, it then became the function of the public health authorities and of the community in general to take preventive action. Enough was already known about many mental health problems to enable preventive action to be taken by the community, and it was for them to take up the challenge where the doctors had shown the way.

Dr. EL KOUSSY (Egypt) discussed mental health in education in a changing world. He felt that orthodox methods of education were producing a race of people who were unable and unprepared to face the practical issues of life. He advocated adding a course on human relations to the school curriculum. Mrs. ELEANOR ROOSEVELT spoke on the individual citizen's responsibility in mental health. Professor OZERETSKY (Leningrad) read a paper on the development of child psychiatry in Russia. Dr. G. BROCK CHISHOLM (Canada), lately director-general of the World Health Organization, spoke of "Some Mental Health Frontiers that Need Attention." Finally there was a special session at which three Russian delegates gave papers on various aspects of mental health in the U.S.S.R.

Technical Discussions

During the mornings the various technical sections discussed a wide programme of subjects of a more specialized character. One section studied the epidemiology of mental disorder. Dr. A. T. M. WILSON and Dr. R. TREDGOLD (London) took part in a discussion on industrial mental health and human relations. Dr. MACLAY spoke on "Community Health Services," and Dr. T. P. REES on "Hospitalization Policies and the Rehabilitation of Patients." Problems of the older-aged citizen, alcoholism, and drug addiction were also dealt with. Another section discussed the mental health of children and youth. Dr. MARY BURBURY (Leeds) contributed to a discussion on the mental health needs of early childhood, and other aspects debated were mental health in education, the mental health approach to teacher education, and the special mental health needs of handicapped children. Dr. ALFORD gave a paper on "The Mental Health Aspects of Mental Deficiency."

Mental health in Governmental activities was the theme of another technical section. This section studied the relationship of mental health to such world problems as technological advance, "The Changing East," migration and refugees, the administration of justice, juvenile delinquency, and mental hazards in penal institutions. Another subject discussed was the function and organization of mental health societies. Dr. HENRY DICKS (London) gave an interesting paper on the integrity of the family. He said that marriage brought to the surface more latent mental instability than war, and many people who appeared socially and industrially capable broke down in their marriage relationships. It was essential, he declared, to keep the family as the unit of community life. He went on to emphasize the place of the father in the home: the importance of his relationships with his wife and children had hitherto not been adequately taken into account. It was the father's reactions that largely decided the mother's attitude towards both her home and her children.

Dr. J. R. REES and Dr. F. CALDERONE, of the United Nations, New York, spoke on the relationship of the voluntary mental health society to international Governmental agencies, and pointed out how valuable was the advisory role of voluntary organizations in relation to bodies such as W.H.O. and Unesco.

The last section took biological adaptation as the topic for discussion, and Dr. HANS SELYE (Montreal) gave a paper on his theory of the general adaptation syndrome in its

relation to mental health. Psychosomatic illness was also discussed by Dr. ERIC WITTKOWER (Montreal) and Dr. CARLOS SEGUIN (Peru) among others. Other subjects were learning and psychotherapy, and operative factors in effective therapy, in the debates on which Dr. AUBREY LEWIS (London) took part as chairman of the panel.

The round-table discussions included "The Importance of the Teacher in Mental Health," "Mental Health Problems and Human Relations in the Classroom," "Is Teaching a Hazardous Profession from the Mental Health Standpoint?" "Parent Education, its Aims and Objectives," and "The Role of the Volunteer Worker in Mental Health." There was also an interesting programme of mental-hygiene films dealing with such subjects as childhood, group psychotherapy, mental illness and treatment, and cultural and social issues.

Associated Meetings and Closing Session

The International Institute on Child Psychiatry held a two-day Congress on August 13 and 14, and the first International Congress on Group Psychotherapy took place on August 12 and 20, both of which were held in association with the main congress. The seventh Annual Meeting of the World Federation for Mental Health was held on August 17, when Dr. FRANK FREMONT-SMITH, Director of the Josiah Macy Jr. Foundation of New York, was inducted as President for 1954–5. Dr. HENRY DICKS was elected as an alternate member of the executive. Professor Dr. F. K. GOKAY, Governor Mayor of Istanbul, Turkey, conveyed an invitation to the World Federation to hold its next annual meeting in Istanbul, probably in the autumn of 1955. This invitation was accepted with acclamation.

At the closing session of the Congress, on August 22, Dr. J. R. REES declared that maintaining mental health was one of the most important contributions to world peace. A mentally healthy nation would be mature and well-balanced enough to be able to understand the problems of other nations without animosity. He felt that the Congress had been of much more scientific value than previous meetings. It had abundantly served the purpose of making valuable personal contacts between peoples of all races, creeds, and disciplines. He believed it would prove a stimulus to all those who had participated in it and would encourage them to return to their homes and spread the gospel of mental health.

Preparations and Appliances

DRIP WOUND RETRACTOR

Dr. A. L. GRIFFITHS, Surgical Registrar, Royal Liverpool Children's Hospital, writes: I am encouraged by Sir Heneage Ogilvie's decription of a thyroid retractor (*Journal*, June 5, p. 1319) to describe a rather similar and equally useful retractor which I designed and made several years ago to aid the exposure of the vein when cutting down for transfusions in infants and children. It is made of 15-gauge stainless steel wire by bending to the shape shown with a fine pair of pliers. Piano wire is more springy but rapidly becomes corroded. The one illustrated is 1½ in. long (3.7 cm.) and intended for neonates, but a slightly larger one is more suitable for larger children with a lot of fat. The need for cheapness is emphasized by the rapidity with which the retractor may be lost—which is inversely proportional to the efficiency of the ward on which it is used. I have also recently seen an ophthalmic instrument on the same principle. *Nihil est dictum, quod non est dictum prius.* I would like to thank Mr. Rodney R. Green for the photograph and Dr. C. H. Jones for the Latin tag.

Nova et Vetera

IN MEMORY OF CAESAR BOECK (1845–1917)

In May, 1954, Dr. Niels Danbolt, professor of dermatology at the University of Oslo, gave an account on the Norwegian wireless of his distinguished predecessor, Caesar Peter Möller Boeck. Everyone has heard of Boeck's sarcoid or sarcoidosis, but few outside the Scandinavian countries know much about the man himself. Professorships were not very rare in the Boeck family. Caesar had two uncles; the one, Christian Boeck, was professor of physiology. The other uncle, Wilhelm Boeck, was the first professor of dermatology at the University of Christiania, his nephew's immediate predecessor. Uncle Wilhelm (often referred to in his nephew's lectures as "the great Wilhelm Boeck") enjoyed an international reputation largely based on a prodigious fallacy. He believed that the soft sore was a mild and harmless form of syphilis, to be employed as a preventive of the serious late complications of syphilis. With the interaction of cowpox and smallpox in mind, he built up an international reputation on his "biological" method of treating syphilis, and in 1865 he was invited to demonstrate it in London, where hospital beds were put at his disposal for this purpose. Uncle Wilhelm's method had been abandoned when his nephew (at the age of 44 years) succeeded him in 1889 as head of the skin department of the Rikshospital in Christiania (the Oslo of to-day).

Caesar Boeck came to dermatology in its "descriptive" phase, and his highly developed sense of form and colour stood him well as he pinned down his impressions on paper. He had inherited from his uncle the fallacy (or what was often held to be a fallacy) that mercury was contraindicated in the early stages of syphilis for fear of impairing the organism's own curative properties. Between 1890 and 1910 close on 2,000 syphilitics were treated at the Rikshospital on this principle, with iron, small doses of quinine, good feeding, and rest displacing mercury. Boeck's successor, Professor Bruusgaard, and others have investigated the subsequent fate of these syphilitics and have shown the extent to which they developed the late sequels of this disease. Boeck combined his hospital work with a large private practice, which cannot have been very remunerative, as his fees were ridiculously small even for those days. His customary fee was two kroner (just over two shillings), but he often reduced it to one-eighth of this sum. However, when patients irritated him by complaining of the inefficacy of his drugs, he took gentle revenge by raising his fee to three kroner. His glowing belief in some of his drugs raised a smile among his students when, in spite of the nakedness of his own billiard-ball scalp, he confidently predicted a cure for patients whose own scalps were threatened by the same complaint. There was no humbug about this. It was just that he let his benevolent optimism run away with him.

It was in 1897 that Boeck first demonstrated a case of the disease which now bears his name. The demonstration took place at a meeting of the Medical Society of Christiania, and the patient was a 34-year-old policeman. Boeck pointed out that the clinical appearance and microscopic structure of the numerous nodules in the skin did not conform to any already recognized condition. He was categorical over the histological features characteristic of this lesion. "A glance through the microscope is sufficient for the diagnosis." Commenting on this claim, Professor Danbolt said: "Boeck was right in so far as the microscopical examination of a suspect process in the skin is a useful aid to the diagnosis." He went on to add: "But later research has shown that there are many cases of this disease in which the microscopic structure of the tissues cannot with certainty be distinguished from morbid processes of quite another character, tuberculosis for example." How simple and straightforward things were in Boeck's days! Boeck was lucky in being allowed to keep going to the end. His latest publication was still in the press when he died of a heart attack after only a few days' illness.

CLAUDE LILLINGSTON.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Blood Groups and Disease

SIR,—In their study showing an excess of blood group A in stomach cancer Aird, Bentall, and Fraser Roberts[1] used hospital patients as controls. In their subsequent study (*Journal*, August 7, p. 315) confirming an excess of blood group O in peptic ulcer, Aird, Bentall, Mehigan, and Fraser Roberts pointed out the danger of such a choice, and chose mainly blood donors as controls. This change assumes that donors are typical of the general population, but this is questionable on two grounds. First, donors may be, on average, somewhat different from the rest of the population in personal temperament, and much has still to be done on the correlation of temperament with physical type, and of both with liability to particular forms of disease. Secondly, only volunteers in the best of health are accepted as donors; there are few who have recovered from serious illness in adult life; and volunteers who have had certain diseases at any time are excluded from the panel, while pregnant women and nursing mothers exclude themselves. Therefore the medical history of donors in general differs, perhaps quite markedly, from that of the population as a whole. Thus, certain diseases having been found to have a substantial association with certain blood groups, the distribution of the blood groups in donors may also differ from that of the population as a whole.

Even if donors do have the normal group distribution, their use as controls might still have pitfalls. For instance, were Darlington's[2] view confirmed that blood group incidence may vary with social class the donors and patients would have to be matched for occupation, the more so as many diseases are partly or entirely occupational (Fraser Roberts[3] has found no evidence in support of Darlington's view in one English district). Again, recent evidence[4 5] suggests that changes with age in the sex-distribution of donors may differ in different groups, and if this were confirmed the donor controls would have to be matched with the patients for age, more especially as the occurrence and forms of disease show great variation with age and sex. In any event, the use of donors as controls should presumably be consistent, and in view of this it is unfortunate that as controls for their London patients Aird and his colleagues should have chosen pregnant women. It is doubly so when there is evidence that the blood groups may influence reproduction—part of which evidence the authors refer to, though they also give a somewhat misleading impression of the classical findings of Hirszfeld and Zborowski.[6] True, the group distribution of these women, as the authors state, is not significantly different from that of the donors of southern England as a whole in 1940, but this ignores the possibility of local variation such as Fraser Roberts[7] has shown to be so marked in northern England.

The importance of knowing for certain whether donors as a class, and donors divided by age and sex, have the normal blood group distribution can be seen from Aird and his colleagues' series of 2,745 cases of stomach cancer. Here the proportion of A to B is significantly high, and this leads the authors to state that B is at an unqualified advantage in stomach cancer. The percentage of B (7.76), however, is only 1% lower than that in the donor controls (8.79), and if the percentage of B should prove to be higher in donors than in the general population the advantage of B in cancer of the stomach may be found to be only relative. In the 1,000 cases in which the sex of the patient is known the percentage of male B's (9.6) is actually *higher* than that of the donor controls (of unstated sex-distribution) and the percentage of B females lower (6.0). Thus, even if the percentage of B in donors should be the same as in the general population, it may be found that, while female B's are at an advantage, male B's are at a disadvantage in cancer of the stomach. (Some support for this possibility, to offset the small numbers concerned here, would be obtained from confirmation of the findings[4 5] of a low sex-ratio in B donors in the later decades of life.) In fact, the over-all shortage of B's in the authors' series of stomach cancer is relatively much less than the excess of B's (at the expense of all the other groups) in their series of cases of cancer of breast and bronchus. Though the smaller numbers—1,017 and 998 respectively—make this excess of B insignificant statistically, a further test might be justified.

If donors did not in fact have the normal distribution of the blood groups the theoretical and practical problems of finding the true normal group distribution would be very time-consuming. Therefore it may be useful to consider whether other ways of investigating blood-group distribution in disease could have validity and value. One such method would be to ascertain the group, sex, age, occupation, and medical history of all the transfusion patients—and ultimately the other patients also—in the principal British hospitals, and then to note the incidence of each blood group in each disease in each region. This done, each blood group would be studied on its own, and if the incidence of that group in the different diseases were found to vary in a way which was significantly alike in the different regions, being high in some diseases in most of the regions, intermediate in other diseases, and low in the rest, there would emerge a pattern of relative liability, neutrality, and immunity to diseases (or perhaps to types of disease) in that group. This particular approach, whatever its merits or (more probably) its faults, would need to be centrally directed, but if there is reason for a nation-wide, centralized study—namely, the Nuffield Blood Group Survey—of the incidence of the blood groups in donors there would seem to be a case for a similar study of the incidence of the blood groups in hospital patients. At the least it would make possible uniformity of method and would guarantee economy of effort, while nothing less would give results within a reasonable time in any but fairly common diseases.—I am, etc.,

Aberdeen. T. M. ALLAN.

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2. "Blood Groups and Mating Groups," 1951, contribution to Symposium on Blood Group Distribution, Royal Anthropological Institute.
3. *Heredity*, 1953, 7, 361.
4. Allan, T. M. (1953). *Lancet*, 2, 456.
5. —— (1954). Ibid., 2, 292.
6. *Klin. Wschr.*, 1926, 5, 741.
7. *Man*, 1951, 51, 94.

Physique and Performance

SIR,—As a Cambridge man I have always associated with the fine-sounding word "Sheldonian" that dignified building whither Oxford men of all shapes and sizes proceed to their degree, unfortified by the rites of somatotyping. If it is really necessary for the aspiring Oxford undergraduate of the future first to be classified according to bodily configuration, may I plead for the "Sheldon" type of somatotyping? And may I further pray that Cambridge will for ever open her doors to all sorts and conditions of men, "polymorphs" and "amorphs" alike?—I am, etc.,

London, S.W.7. W. DYKES BOWER.

SIR,—Some bold spirits would go further than Dr. R. W. Parnell in his article (*Journal*, August 28, p. 491). For example, it has long been known that the populations of the world in general, and of certain areas in particular, are limited by their food supply and raw materials. There are those who regard Malthus's original contention as an accurate prediction. Moreover, individuals vary enormously in their physique and temperament.[1 2] I wish to put forward a plea for a study of the genotype of the individual in the choice of individuals studying in any faculty of a university, and particularly should this apply to the choice of medical students. Needless to say that existing knowledge of genetics is inadequate; but is it not time to devote further money and research to this particular influence on the choice of medical students, and to the investigation of the world population? Who are to be the choosers?

Nobody yet knows enough genotypology, so that existing methods (case history, medical examination, interview, psychometry) will have to be employed in the meantime.—I am, etc.,

Winscombe. ROBERT L. SIKES.

REFERENCES

1 Sheldon, W. H., and Stevens, S. S. (1942). *The Varieties of Temperament*. Harper, New York and London.
2 —— —— and Tucker, W. B. (1940). *The Varieties of Human Physique*. Harper, New York and London.

Smoking and Lung Cancer

SIR,—Dr. K. Blond's letter (*Journal*, July 31, p. 303), in which he seeks to minimize the dangers of cancer of the lung in smokers, contains the following sentence: "The distribution of cancer is constantly shifting from one organ to another, but the total incidence of cancer remains about equal." Dr. Blond therefore argues that to escape from the Scylla of cancer of the lungs is but to fall into the Charybdis of cancer, shall we say, of the stomach. The fallacy, as I see it, in this argument lies in the fact that even if the incidence of cancer remains the same, which I understand from the evidence is not true, the total number of years lived certainly does not remain the same. Let us suppose that we all lived indefinitely, then, as cancer increases steadily with the age, eventually, if we did not die of something else, we should presumably all die of cancer somewhere or other. *But the more cancers we avoided, the longer we should live.*

Take the following example: Let us imagine a group of five men. Of these, three men die of injury, nephritis, and phthisis, respectively. The other two worked exposed to β-naphthylamine and both would have died of cancer of the bladder, but as it happened only one did, because one left this occupation for another before any harm ensued. Twenty years later, at the age of 60, this man developed cancer of the colon, which was successfully removed by operation. At the age of 100, however, he developed cancer of the throat, and that killed him. The incidence of fatal cancer at the end was the same as it would have been at the beginning—40%. But as the result of avoiding one cancer and curing another an extra 60 years of life resulted. It seems vital, in the drive to prevent and also to cure this dreaded disease, that this fallacy in the above argument should become well known.—I am, etc.,

Alverstoke, Hants. T. L. CLEAVE.

Infant-feeding

SIR,—I was very interested to read Dr. Arnold George's comments (*Journal*, August 28, p. 535) on an infant-feeding advertisement in your July 17 edition. I submit that it is impossible to write any article on this controversial subject without arousing criticism. Dr. George has quoted such eminent authorities as Dr. Charlotte Naish, Professor R. S. Illingworth, and Dr. Ian Wickes. May I now, to illustrate my point, quote a few more authorities, who appear to hold different points of view?

(1) Dr. W. Sheldon[1]: "Consecutive feeds should always begin on alternate breasts." (2) Dr. J. Gibbens[2]: "On the fourth day the flow of milk should be established." (3) Dr. D. Paterson and Professor A. Moncrieff[3]: "The daily weighing of the newborn infant is therefore of extreme importance, and test feeding is quite necessary." (4) Drs. P. R. Evans and R. Mac Keith[4]: "Some babies gain well on less than this well-known figure (2½ ounces (7 g.) per 1 lb. (0.45 kg.) weight), and a contented baby need not be forced to take more than he wants." (5) Dr. W. R. F. Collis[5]: "The average gain per week is 4–6 ounces (113–170 g.)." (6) Dr. Collis[6]: "Classification of Constipation . . . obstruction, protein dyspepsia, overfeeding . . ."; and Dr. Bruce Williamson[7]: "Signs of overfeeding . . . 3. Bowel disturbance may take the form of diarrhoea or constipation, according to the nature of the diet."

I hope, Sir, that these quotations may show the wide variance in opinions held by leading authorities on the subject and illustrate that the views expressed in the advertisement are a reasonable cross-section of medical opinion.—I am, etc.,

Guildford. R. A. DE K. GLOVER, Medical Adviser, Cow & Gate, Ltd.

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1 *Diseases of Infancy and Childhood*, 1951, 6th ed. Churchill, London.
2 *The Care of Young Babies*, 1950, 3rd ed. Churchill, London.
3 *Diseases of Children*, 1947-9, 4th ed. Arnold, London.
4 *Infant Feeding and Infant Difficulties*, 1954, 2nd ed. Churchill, London.
5 *Modern Methods of Infant Management*, 1948. Heinemann, London.
6 Ibid., 1948. Heinemann, London.
7 *A Handbook on Diseases of Children*, 1953, 7th ed. Livingstone, Edinburgh.

Explosions of Bowel Gas

SIR,—Your annotation on the above subject (*Journal*, August 21, p. 459) was timely and gives deserving publicity to the little-known fact that combustible anaesthetics are not the only causes of fires and explosions in operating theatres. It would appear that your annotator and I have both been thinking along the same lines. Early in 1953 a joint subcommittee was appointed by the Medical Defence Union Ltd. and the Council of the Association of Anaesthetics of Great Britain and Ireland to study the causation and prevention of fires and explosions in operating theatres. Later in the year most of this committee was included in a working party appointed by the Ministry of Health to investigate the same problem. To both of these committees (to which I was appointed as a member) I submitted a memorandum similar in nature to your annotation. This was seen by Dr. T. Cecil Gray, who asked me to rewrite it "as amusingly as possible" for the *British Journal of Anaesthesia*, of which he is joint editor. This I did, and the article appeared in the May number of that journal this year. When reading your annotation I was surprised, therefore, to find that your annotator had referred only to part of my article and gave no indication that I had also mentioned all the other items listed in his annotation.—I am, etc.,

West Ewell, Surrey. A. H. GALLEY.

Tooth-protector for Laryngoscope Blade

SIR,—Dr. F. F. Waddy describes (*Journal*, July 24, p. 239) a rubber attachment to fit over the blade of a Macintosh laryngoscope to protect the teeth during laryngoscopy. I have previously described[1] a modification of both the Macintosh and Soper laryngoscope blades designed for this very purpose, and in which a strip of rubber is stuck on to the upper shelf of these blades with "bostik" adhesive. This has proved perfectly satisfactory in practice and is simpler, I think, than the attachment described by your contributor.—I am, etc.,

London, W.1. R. BLAIR GOULD.

REFERENCE

1 *Anaesthesia*, 1954, 9, 125.

SIR,—Dr. F. F. Waddy's description of a rubber tooth-protector for attachment to the Macintosh laryngoscope blade (*Journal*, July 24, p. 239) prompts me to suggest an alternative method of avoiding damage to the incisor teeth which I have been using here for some time. It is simple and inexpensive in the extreme, and consists only in the application of a small strip of "elastoplast" about ¼ in. wide by 1½ in. long (1.2 cm. by 3.7 cm.) to the blade of the laryngoscope. A double thickness can be used if desired, and there is no risk at all of dislodgment, which is a possibility with Dr. Waddy's protector: after use the strip is discarded and a new one can be applied in next to no time.

Some form of protection from the metal laryngoscope blade is essential when dealing with the local population (largely Chinese and Indian), whose standard of dental hygiene is very poor indeed, and it was a particularly friable tooth in an otherwise easy patient which first directed my attention to the matter. Since using the "elastoplast" strip I believe I have only caused damage to the teeth in one instance: on this occasion I removed a loose incisor with my fingers before proceeding with intubation.—I am, etc.,

Taiping, Malaya. A. S. GARDINER.

Pitocin in Obstetrics

SIR,—With due respect to Dr. G. W. Theobald, the originator of the "pitocin" drip technique, I must reply to his rather severe criticism (*Journal*, August 14, p. 413) regarding the dosage of pitocin used in my unfortunate case of cardiac arrest under light cyclopropane anaesthetic with pitocin drip (*Journal*, July 10, p. 79).

Thirty units of pitocin were injected into about 900 ml. normal saline to make the uterus contract quickly—that is, within five minutes. The rate of the drip was about 30 drops per minute, and after adding the pitocin it ran for slightly less than two minutes before it was stopped because of the condition of the patient. In these two minutes she could barely have received 0.25 of a unit of pitocin. Five units of pitocin are frequently given either intramuscularly or intravenously for post-partum haemorrhage, without any reported fatalities, but these cases are usually either fairly deeply anaesthetized or wide awake. Such a small dose of pitocin administered in my case could hardly be the main cause for the fatal cardiac arrest.

I would add that, after some years of experiment with various dosages of pitocin in the drip, we concluded that 30 units per litre was the optimum concentration to initiate uterine contractions quickly. The rate of administration was usually 15 drops per minute. This concentration was used in about 200 inductions, and very rarely did we see uterine spasm and never a maternal death.—I am, etc.,

London, S.E.5. MARTIN LESSER.

A Plastic Surgical Dressing

SIR,—On my return from abroad, I read with interest the report on the use of a solution of acrylic resin in solvents by Messrs. C. G. Rob and H. H. Eastcott at the surgical unit of St. Mary's Hospital (*Journal*, July 3 p. 17). The application is not novel, nor can the product compare in surgical value with "portex," which has been used for the same purpose for many years.

Portex is a combination of acrylic resin with phenyl salicylate, resorcin and eugenol, also insolvents, and is ten times as adhesive, elastic, vasoconstrictive, and analgesic as the pure resin alone. Its use as a surgical barrier and dressing was investigated by Mr. H. W. S. Wright and fully reported in the *Lancet*[1] after 300 operations, and many thousands of surgeons who have used the product will support his findings. The use of a solution of acrylic resin which is not even germicidal is a retrograde step rather than an advance in medical science, and calls for comment.—I am, etc.,

Hythe. S. A. LEADER.

REFERENCE

1 *Lancet*, 1944, 1, 664.

Negative-pressure Drainage in Radical Mastectomy

SIR,—I read Mr. G. F. Cassie's account of the above with interest (*Journal*, August 21, p. 452). I have used a somewhat similar method for the past three years, and can confirm all the advantages claimed for the method. Instead of negative-pressure drainage, however, I have used continuous suction, the tube being connected to the usual three-bottle suction apparatus, which we use for gastro-intestinal suction. This gives excellent results, and is continued for six days. At the completion of the operation the drainage tube is stitched to the skin to give an airtight function, and then all the air is very easily removed from beneath the flaps by applying the sucker to the tube. The flaps immediately sit tight on the chest wall, and the most dramatic part is the way the skin clings to the axillary vault, which is most important for early and sound healing. The tube is then clipped off free attached to the sucker apparatus on return to the ward. The method has without doubt removed many of the unpleasant features during the convalescence after radical mastectomy.—I am, etc.,

London, S.E.13. JAMES JEMSON.

Persistence of Actinomycosis

SIR,—Actinomycosis of the abdomen is a comparatively rare and, until recently, a fatal disease. Armitage and Smith, however, in their recent review[1] have shown that with modern chemotherapy the prognosis has greatly changed for the better and survivals may now be expected. But the tendency for infection by actinomyces to persist, though perhaps in a quiescent condition, should be kept in mind when assessing prognosis or describing a case as "cured." A recent patient of ours has again brought the importance of this feature to notice.

A man of 26, following the removal of his appendix and drainage of an appendix abscess on June 4, 1952, developed a subphrenic abscess which contained *Streptothrix actinomyces*. He made a good recovery after drainage of his subphrenic abscess on June 30, 1952, and exhibition of aureomycin, as we reported elsewhere.[2] An abscess developed in the appendicectomy scar and ruptured spontaneously on March 1, 1953. At operation on May 15, 1954, for a ventral hernia which had developed in the appendicectomy scar, Mr. W. P. Small found a small abscess undetected clinically in the muscles at the medial end of the wound. From this abscess, as from the previous ones, Dr. Helen A. Wright, of the Bacteriological Service, Edinburgh University, isolated Gram-positive filamentous branching organisms typical of an actinomyces. Following the operation for repair of the incisional hernia, the patient was given aureomycin, 1 g. daily in 250-mg. doses six-hourly for seven days. He made an uninterrupted recovery and now has a sound abdominal wall. He has been in excellent health since March, 1953, performing his full duties as a post-office sorter, lifting and carrying heavy mailbags. This repeated straining, in fact, led to the development of the hernia in his weak appendicectomy scar, necessitating repair. The opportunity was thus afforded for checking up on the site of the old infection, with the result described.

The streptothrix has not given rise to any trouble in this case for over a year, and the finding of a small abscess in the abdominal wall was, in fact, a surprise. But the fact that an actinomyces has been isolated again shows that though modern chemotherapeutic agents, in this case aureomycin, undoubtedly saved the patient's life and restored him to good health, the actinomyces still persists and may perhaps in a subsequent period of lowered resistance again give rise to trouble. A careful follow-up in these cases, and the co-operation of the bacteriologist, is essential.—We are, etc.,

Edinburgh. JAMES A. ROSS. IAN C. S. KNIGHT.

REFERENCES

1 *Brit. J. Surg.*, 1954, **42**, 77.
2 *Edinb. med. J.*, 1954, **61**, 170.

Normal Cerebrospinal Fluid Sugar in Tuberculous Meningitis

SIR,—The concentration of sugar in the cerebrospinal fluid is now considered to be far more important than that of chloride as an aid to the diagnosis of tuberculous meningitis. Indeed, most authorities think that it is of paramount importance in the differentiation of this disease from poliomyelitis and other lymphocytic meningitides. A recent case, however, has shown that the sugar concentration can be normal when there is convincing evidence of active tuberculous infection being present. The cerebrospinal fluid findings on three occasions are shown in the table.

	June 21, 1954 (First Specimen)	June 22, 1954	June 25, 1954
Leucocytes total/c.mm.	132	184	253
Polymorphs/c.mm. ..	78	19	61
Lymphocytes/c.mm. ..	52	165	192
Macrophages/c.mm. ..	2		
Protein mg./100 ml. ..	65	75	75
Globulin	Slight increase	Slight increase	Slight increase
Chloride mg./100 ml. ..	632	602	554
Sugar mg./100 ml. ..	51	64	64
Z.N. film	No acid-alcohol-fast bacilli	One a.a.f.b. seen	Scanty a.a.f.b. seen
Culture for *Myco. tuberculosis*	Positive	Positive	Positive

Neither streptomycin nor isoniazid had been given before any of these examinations were undertaken, because the "one acid-alcohol-fast bacillus" seen on June 22 was regarded with some suspicion. The method of sugar estimation used was that of Folin and Wu. Fresh standard is made up every day from a stock concentrated standard glucose solution which is renewed every month. Checks are periodically made upon the accuracy of the method by examination of specimens of blood, the sugar concentration of which has been determined by the biochemist at another hospital in the area. All specimens of cerebrospinal fluid for sugar estimation were put into bottles containing sodium fluoride (to prevent glycolysis) at the time of the lumbar puncture. The patient is now recovering after being on treatment, and, on clinical grounds, Dr. S. R. Jamieson (to whom I am indebted for permission to publish) is convinced that she is a case of tuberculous meningitis. There is no proof that the patient's blood sugar was not high at the times that the specimens of cerebrospinal fluid were taken. However, urine examinations showed no evidence of sugar and the patient has no symptoms of diabetes mellitus. Furthermore, later specimens of cerebrospinal fluid have showed a lowered sugar level—for example, 38 mg./100 ml.

Cruikshank[1] states that, of 137 cases in which the sugar content of the first sample was estimated, the figure was never higher than 50 mg./100 ml. Furthermore, writing in such an authoritative work, he makes no mention of the fact that the sugar level can be normal. Lewis[2] found that none of a series of 65 specimens gave a figure of more than 50 and that a level of less than 20 mg./100 ml. was found in more than half the specimens. He emphasizes that a fall in the sugar content is an early finding. This view is, however, not held by Stitt *et al.*,[3] who state that tuberculous meningitis causes a gradual fall. My colleague, Dr. M. G. Philpott, informs me that at the University of Sheffield normal cerebrospinal fluid sugar levels were occasionally seen in active tuberculous meningitis.

The work of Goldring and Harford[4] and that of Weichsel and Herzger[5] has shown that there is insufficient evidence in bacterial meningitis to support the theory that the lowering of the cerebrospinal fluid glucose is caused entirely by the consumption of the glucose by leucocytes and bacteria. Sifontes *et al.*[6] have produced evidence to support the theory that lowering of the sugar level in the cerebrospinal fluid in tuberculous meningitis may, at least partly, be due to an alteration in permeability of the blood–cerebrospinal fluid barrier. It seems possible that this alteration in permeability may not be present in every case.

No originality is claimed for this observation, but it is believed that the fact that a normal sugar level in the cerebrospinal fluid in active tuberculous meningitis sometimes occurs is not widely known.—I am, etc.,

N. Ferriby, Yorks. J. G. ALEXANDER.

REFERENCES

1 In *Recent Advances in Clinical Pathology*, 1951, edited by S. C. Dyke, 2nd ed., p. 33. Churchill, London.
2 *British Medical Journal*, 1948, 2, 1036.
3 *Practical Bacteriology, Haematology, and Parasitology*, 1948, 10th ed. Lewis, London.
4 *Proc. Soc. exp. Biol. (N.Y.)*, 1950, 75, 669.
5 *J. Pediat.*, 1936, 9, 763.
6 *Amer. Rev. Tuberc.*, 1953, 67, 732.

Contact Lenses

SIR,—I would like to add a few remarks to Dr. J. M. Anderson's letter (*Journal*, August 28, p. 534) commenting on your annotation on the subject of contact lenses. In my experience the type of contact lens and the material used is not of very great significance. What is necessary is that the patient should be able to wear the appliance for fairly long periods with comfort and without any corneal oedema developing. There is very strong evidence that corneal oedema develops as a result of impairment of nerve control of the cornea due to irritation or presence of noxious substances in the precorneal fluid.[1] I feel that one should not confine oneself to any particular type of lens: some patients do well with glass lenses, some with preformed plastic, some are happy with corneal caps, etc. Each case must be dealt with on its own merits. Wearing-time in stuffy atmospheres can be increased a lot by improving the exchange of precorneal fluid. To do this successfully a good fit and very good balance is absolutely essential; unfortunately good balance cannot be achieved in a corneal lens.—I am, etc.,

Oxford. M. SARWAR.

REFERENCE

1 Sarwar, M. (1953). *Trans. ophthal. Soc. U.K.*, 73, 547.

The Treatment of Pertussis

SIR,—I have this year seen a number of undoubted second attacks of pertussis after successful early treatment of the initial attack with chloramphenicol. This poses a number of problems, for which I am unable to find the answer within the limits of my own practice.

The earlier treatment is started the more likely it is to be effective, and it is probably useless after the first ten days; but, on the other hand, my experience suggests that early treatment may prevent the development of immunity. It would be interesting to know whether it is indeed possible to time the beginning of treatment so that the infection is suppressed and yet immunity is subsequently developed. This raises the question whether it would be advisable to administer vaccines to patients being treated with antibiotics, and, if so, what would be the best timing and dosage. On the answer to these questions depends the problem of whether to treat all early cases of pertussis with antibiotics, or whether to reserve it for very young and delicate children. I would be interested to hear the views of other practitioners on these problems.—I am, etc.,

Kenilworth. R. E. DANCKWERTS.

Selection of Medical Students

SIR,—To your discussion on medical education may I say this. However much I understand this insistence on autonomy of choice of the different universities, I think it is quite unnecessary to have 12 different selection boards representing 12 medical colleges in one university like London. A university ought to be one organic structure whose standards for admission to any of its specialized studies ought to be standardized.—I am, etc.,

Cockfosters, Herts. F. GUGENHEIM.

Cancer and Available Soil Copper

SIR,—Dr. E. D. Allen-Price (*Journal*, October 11, 1952, p. 831) called attention to the excessive gastric cancer mortality in the Tamar Valley. I have found that over much of the area the level of available copper in the cultivated soil is only 1.9 parts per million. I am informed by an authority on minor element deficiencies that even 5 p.p.m. is to be considered as rather low. An attempt is being made to enlist the interest of market-gardeners for the solution of the broad problem raised by this finding.—I am, etc.,

London, S.W.17. C. D. LEGON.

Fractures Complicating E.C.T.

SIR,—With reference to recent correspondences on this subject, it is generally agreed that fracture of the spine following E.C.T. is not a serious injury. The type of fracture is similar to that found in cases of psychosis with chronic epilepsy, although the site may be different. Two types of fracture occur—namely, the anterior wedge fracture and the "disk repercussion" fracture, which shows as a depression of the superior surface of the vertebral body on the lateral view, and as a horizontal line of increased density on the antero-posterior view. The fracture most often occurs in the upper and mid-thoracic spine, the commonest site being T 4, 5, or 6. They are always confined to the vertebral bodies, and I know of no reported case of cord damage. However, a fracture of the neck of the femur or upper humerus may be a serious injury in these patients. The incidence of fracture of the neck of the femur is low (0.7%), but when it occurs it is sometimes bilateral, one such case dying within 24 hours of acute pulmonary oedema.[1]

Injuries to the shoulder vary from an avulsion of the greater tuberosity to a comminuted fracture dislocation of the upper end of the humerus. Sometimes the dislocation of the humeral head is posterior and difficult to reduce in the presence of a comminuted fracture of the upper humerus. To prevent such complication, any restraint of the upper limbs considered necessary during the convulsion should be applied not to the shafts of the humerus but to the front of the glenoid. As previously stated (*Journal*, July 10, p. 98), the incidence of fracture following E.C.T. is not great, but the consequences depend a good deal on the part involved. Fracture-dislocations of the upper humerus and fractures of the femoral neck cause the greatest concern.—I am, etc.,

Lancaster. J. P. KELLY.

REFERENCE

1 Kelly, J. P. (1954). *J. Bone Jt Surg.*, 36B, 70.

POINTS FROM LETTERS

Acute Post-operative Laryngeal Obstruction

Dr. P. M. MEHTA (Rochford) writes: May I add one more probable predisposing cause of acute laryngeal obstruction to those given by Drs. J. B. Prendiville and H. G. Middleton (*Journal*, May 15, p. 1126)? Oedema due to hypoproteinaemia—a subclinical one—is often associated with cases of burns. And we see from the history of the cases that Drs. Prendiville and Middleton report they were subjected to operation after four to six weeks, so a considerable amount of protein loss must have occurred during this period. I think, before subjecting the patient to operation, the plasma protein content should be investigated, and corrected to normal level if it is deranged.

Smoking and Cancer

Mr. A. P. BERTWISTLE (Birmingham, 28) writes: Your inclusion of a paper on mortality and smoking by Dr. Richard Doll and Professor Bradford Hill, two medical statisticians (*Journal*, June 26, p. 1451), and "The Role of Smoking in Bronchitis" by Dr. K. N. V. Palmer, a physician (p. 1473), is indeed opportune. The more one thinks of cancer the more one feels that it has an inflammatory background. . . . Is it too much to ask of the statisticians that they analyse their figures to find out the percentage of bronchial cancers among bronchitics?

Treatment of Status Asthmaticus

Dr. S. W. VIVIAN DAVIES (Camborne) writes: In his letter (*Journal*, July 24, p. 242) Dr. D. D. Vora mentions a major problem in the treatment of status asthmaticus—the removal of tenacious secretion from the bronchi. The plugging of the bronchi is a common factor in all deaths in this disease, and attempts are being made to attack this deadly glue-like substance with liquefying aerosols.

Cure for Baldness

Dr. JOHN KELVIN (Glasgow) writes: Two of my patients to whom I gave β-pyridyl-carbinol tablets ("ronicol") for intermittent claudication proudly and happily volunteered the information that the tablets had grown a good crop of hair on their bald pates. This welcome side-effect is certainly a surprising and hair-raising phenomenon. One patient offered the feasible suggestion that the hirsutic embellishment is due to the tablets improving the circulation of the scalp by their vasodilating action. . . . I would like to add that my patients had had vitamin E tablets ("ephynal" tablets) prior to the administration of ronicol. But regrowth of hair followed only after taking the latter. Patients took one tablet four times daily, and grew hair after taking about 250 tablets. I confess that I have not yet personally tried the tablets to cure my own baldness.

Carcinomatous Obstruction Strangulated in Hernial Sac

Dr. R. T. D. FITZGERALD (Corringham, Essex) writes: An elderly man who for many years had worn a truss for a small inguinal hernia was admitted as an emergency as a case of acute obstruction due to a strangulated inguinal hernia. The diagnosis seemed obvious, and I was on the verge of 'phoning the surgeon, when I decided that there was something suspicious about the irreducible mass: the upper part was acutely tender, but the extremity was quite painless and very hard. Suspicion was converted to certainty when, after careful questioning, the patient admitted that he had vomited once before the mass, which was much larger than his usual hernia, had become irreducible. Proof was found when rectal examination revealed two small hard mobile nodules. The patient had become obstructed owing to his carcinoma of the caecum, which, owing to his subsequent distension and vomiting, had been forced into an otherwise small hernial sac, where it had become irreducible.

Obituary

ALFRED COX, O.B.E., M.A., LL.D., M.B.

The obituary notice of Dr. Alfred Cox, who died on August 31, was published in last week's *Journal* (p. 597). We print below a number of tributes from his old friends and colleagues.

THE CHAIRMAN OF COUNCIL, Dr. E. A. Gregg, writes: In the passing of Alfred Cox we bid farewell to one who occupied an outstanding place in furthering the unity and progress of the medical profession in this country in all its many fields of activity, and also in its relationships abroad. The fine Association we now have, and of which we are quite rightly so proud, owes a very great debt to him as one who was outstanding in the early days of its constitution and consolidation, and who in those difficult times held steadfastly to the principles and ideals on which the Association was built. Adverse criticism, recriminations, and the defection of some never daunted him in his purpose. Forthright and blunt in his utterances often, yet he never harboured rancour or resentment. He was always keenly appreciative of the work of others and generous in his acknowledgments. His letters of congratulation and encouragement never failed to reach those individual members who might from time to time take office of one kind or another in the Association: a little success or achievement was always noticed, and a letter from him was received invariably. This practice of his continued right on to the end. Until his eyesight failed him in the last few months of his life he claimed that he read the *Journal* from cover to cover every week. His shrewd and critical communications from time to time bore out the truth of his claim. Although in ill-health for years past, his interest in the Association, which he did so much to help, never waned, and nothing pleased and cheered him more than to hear news of its advancement.

To the majority of the members of the British Medical Association Cox is a name and a legend. To those of us who knew him right through from the old days in the Strand his name will ever evoke the memory of a man of outstanding singleness of purpose to whom the Association will always owe a very great debt of gratitude.

Lord HORDER writes: To the Editor's request that I should pay my tribute to my old friend there can be only one answer. I say "old" friend because forty-odd years of friendship surely justifies the term. I have read the *Journal's* obituary notice and can say, truly, that every word of this splendid encomium was more than justified. The cliché "*De mortuis*, etc.," suggests that one *could* say things that are not good about the late departed. It would indeed be difficult to say anything that is not utterly good about Alfred Cox. Some folk found him a "hard" man. At first I, a southerner, did myself. But as our friendship ripened—and we had much in common in our outlook on medicine and our profession to bring this about—I changed my view from "hard" to "tough." And much was happening in medicine to require, more than anything else, this element of toughness when our colleagueship began.

The expression "mental integrity" has been much overworked. But it is difficult to avoid its use in the case of Alfred Cox. And I share the view of "an old colleague" who wrote last week (p. 599) that he "was the most single-minded man" he had ever met. That, I think, is my view also, and I have met many men in my time. "This one thing I do," said Paul. Cox could with equal truth say the same of his life's work. This was probably the greatest contribution made by any one man to the history and well-being of the Association that he loved so dearly and served so faithfully.

Dr. H. GUY DAIN writes: With the passing of Alfred Cox the B.M.A. loses one of its oldest members, and

certainly one of its most loyal members. It would be no exaggeration to say that for more than 40 years the B.M.A. was his great interest. In his years of private practice in the North he was most active in the formulation of the present constitution. The Representative Body was largely his child, and he was properly proud of it. Even in very recent years, whenever the A.R.M. was held in London he could usually be seen in the gallery, following the proceedings with complete understanding. When he came to be Medical Secretary he found the B.M.A. and himself involved in the arguments and discussions with the Government over Mr. Lloyd George's National Insurance Act, and at all times "the panel doctor" found in him a very doughty champion. His wisdom and sound common sense were a great asset to the Association on many occasions. He was a cheery soul, and never lost his sense of fun. As a North-countryman of judgment and determination he could maintain his opinions with directness without unnecessary words. Those of us who worked with him over the years knew him as a loyal and completely dependable friend, always ready to hear and consider another point of view. During his 20 years of secretaryship the influence and value of the B.M.A. to the profession, and to the public, were steadily built up on the basis from which the Association has gone forward.

Dr. PETER MACDONALD writes: It is some 50 years since I first became acquainted with Alfred Cox, and the news of his death is associated in my mind not so much with sadness as with joy at having known him. His autobiography ends with these words:

"I have had a happy life and, nearing the end of it, I have much to be thankful for. I can say, as few men can, that I have done just the work I wanted to do and through it have made a host of friends amongst whom have been many of the very salt of the earth."

The truth of these words is the reason I have begun this short testimony to his life and work in the way I have done. He started work as a general practitioner in a small way. Practically the first thing which seriously occupied his activities was the "battle of the clubs." How serious this was has largely been forgotten by modern practitioners. There is neither time nor space for me to enlarge upon it now, but the activities of Cox and others had much to do with bringing it to an end—though it was brought finally to an end by the passing of the National Insurance Act, in the negotiations over which Cox had much to do. Cox was appointed Medical Secretary of the B.M.A. in 1912, and he held this office until he was 66 years of age. He was a great secretary, and his example has had much to do with the "setting of the pace" for the fine secretarial work of the B.M.A. He was a good friend to me, and I, as well as all who knew him, will miss him.

Dr. J. C. MATTHEWS writes: The death of Dr. Alfred Cox is not so much a matter for sorrow and regret, it is rather the occasion for admiration and thankfulness: his life had been one of continued and sustained activity in furthering the welfare of our profession. The need for improved organization was realized during his early years in general practice in the county of Durham. It was here he gained the experience which became the foundation of his life's activities on behalf of the profession, as Secretary of the Association from 1912 to 1932. I have a file into which, through the years, I have placed correspondence and notes of special interest and significance. It was there to-day that I found a letter which Dr. Cox wrote to me in May, 1925, in reference to my election to the Council for the first time. This letter is typical of the hundreds he must have dispatched to members of the Association all over the world. For me it was the beginning of a lasting and much-valued friendship. Some other pen must detail the numerous activities and interests which he maintained after retirement from the post of Secretary. It was a joy to meet him at lunch in the common-room at B.M.A. House from time to time, until, about a year ago, owing to failing health his visits became less frequent.

Mr. C. H. SCRIVENER, chief clerk of the secretarial department of the B.M.A., writes: Among the members of the clerical staff who were privileged to serve under Dr. Cox the outstanding impression was of one who had found his life's work and was completely devoted to it. He was an inspiration to us all. Many of us found that his somewhat severe exterior covered a very kind heart, for he was always ready to listen patiently to our problems, real or imaginary. His advice was well worth seeking. We shall miss his cheerful message at Christmas, for he never forgot us. We salute the passing of a well-loved chief.

B. T. PARSONS-SMITH, M.D., F.R.C.P.

Dr. B. T. Parsons-Smith, who was a physician on the staff of the National Hospital for Diseases of the Heart for 27 years, and dean of the postgraduate medical school there for 24 years, died at Tadworth, Surrey, on September 3, aged 72.

Basil Thomas Parsons-Smith was the son of the late Dr. S. Parsons-Smith, J.P., of Croydon, and studied medicine at St. Thomas's Hospital, where he qualified in 1907. After graduating M.B., B.S. at London University in 1908 he held a number of appointments at St. Thomas's, including those of casualty officer, house-physician, resident anaesthetist, and house-physician to out-patients. He was also anaesthetist to the London Throat Hospital. In 1909 he proceeded to the degree of M.D.

For some years before the first world war he was in general practice in Croydon, but he was interested in cardiology from early on in his career, and during the first world war he was in charge, with the rank of captain, R.A.M.C., of a special centre for men with heart disease at Cayeux-sur-Mer. After the war he published an analysis of 1,000 cases of heart disorder in soldiers. He gave up general practice when he was demobilized, took the M.R.C.P., and was appointed a heart specialist to the Ministry of Pensions and assistant to the heart department at St. Thomas's Hospital. His long association with the National Heart Hospital began at this time, and his first appointment there was as physician to out-patients. He became full physician in 1929 and retired in 1947. He was elected F.R.C.P. in 1929.

Dr. Parsons-Smith was first and foremost a clinician and was president of the Clinical Section of the Royal Society of Medicine from 1936 to 1938. A member of the Hunterian Society for a great many years, he won the Hunterian Medal for an essay entitled "Intermittent Pulse" in 1914. He was president of the Society in 1952–3. He gave the Hunterian Society Oration in 1934, the St. Cyres Lectures at the National Heart Hospital in 1936, and the Lumleian Lectures, on the subject of cardiac failure, at the Royal College of Physicians in 1950.

Dr. BERNARD MYERS writes: The many friends of Dr. Parsons-Smith will have learned of his passing with deep regret. He was not only one of our leading cardiologists, he was also a delightful and charming personality and one of the best of friends. I knew him for over thirty years and felt great admiration for his character and his kindliness in all matters. We were both much interested in the Clinical Section of the Royal Society of Medicine, especially during the early 'thirties, and I can state that he rendered great service to the Section and was invaluable. Parsons-Smith was a first-class clinician, and in addition no trouble was ever too much if he could help a patient. His medical friends who consulted him—and they were many—had good reason to appreciate the value of his opinion and help.

With his cultured mind and kindly heart he endeared himself to all who had the good fortune to be included among his friends. He will be greatly missed.

F. C. BOTTOMLEY, O.B.E., M.D.

Dr. F. C. Bottomley, who was on the honorary staff of the Royal Victoria and West Hants Hospital, Bournemouth, for many years, died at Boscombe on August 21 at the age of 85.

A Yorkshireman, Francis Carr Bottomley was born on January 18, 1869, and was educated at Giggleswick School. As a medical student he had a brilliant academic career, winning a scholarship and the Shuttleworth Exhibition to Caius College, Cambridge, where he took a double first in the Natural Sciences Tripos and was president of the Science Society. Going on to St. George's Hospital with a university scholarship, he graduated M.B., B.Chir. in 1894 and then held a large number of junior resident posts at St. George's, including that of assistant surgical registrar, before he was appointed senior resident medical officer at the Royal Free Hospital. At this time he had a leaning towards surgery and took the Conjoint diploma in 1897. In the following year he proceeded to the M.D. After a period of further study in a number of European capitals he settled in general practice at Boscombe in 1898, his partner being a well-known Bournemouth surgeon, the late Mr. Arthur Heygate Vernon, also a St. George's man.

Bottomley's first appointment at the Royal Victoria and West Hants Hospital was as anaesthetist, but shortly afterwards he was made assistant surgeon, and then a year or two later he became a full physician on the honorary staff—a striking example of the versatility of general practitioners of the old school. In due course he became senior physician at the hospital and one of the most popular and respected medical men in a town which has never been short of doctors of outstanding ability. He served as president of the Dorset and West Hants Branch of the British Medical Association in 1922 and was a vice-president of the Section of Medicine at the Annual Meeting of the Association held at Bournemouth in 1934.

Bottomley retired from the active staff of the Royal Victoria and West Hants Hospital twenty-five years ago, when he was appointed consulting physician, but of course he continued in general practice, for that was work which he found entirely satisfying. His patients venerated him because they knew that their welfare was the be-all and end-all of his life. He examined them carefully, but spoke to them very little, for he was an exceedingly quiet, even silent man: in fact he had been known to enter a patient's house and depart from it without saying more than a word or two. But his reticence never obscured his kindness and sympathy. Until close to the time of his death he continued to see a few of his old patients. After the death of his wife some years ago he lived a quieter life than ever, but he always retained his great interest in medical advances and was a conscientious reader of medical journals and textbooks.

During his early years Bottomley contributed several articles to this and other journals, and in fact his first published paper, on meningitis, was published in the year he graduated. Wrapped up in his work as he was, he had little time for outside interests, but he was a very active supporter of the St. John Ambulance movement. During the first world war he was in charge of an auxiliary hospital in Bournemouth and organizer of hospital transport there—work for which he was appointed O.B.E. in 1920. During the last war he was appointed a Knight of the Order of St. John of Jerusalem, an honour which pleased him greatly.

Dr. C. HEYGATE VERNON writes: I remember Dr. F. C. Bottomley first as a shy young man who joined Arthur Heygate Vernon in partnership some 55 years ago. It would be hard to find anyone who could claim to beat his record of "service before self." He was a shining example of the old-fashioned practitioner who preferred to attend the poor, often for little or no reward, and yet he had the qualifications and attainments of a physician specialist on the staff of the Royal Victoria and West Hants Hospital. Indeed, he had the knowledge and ability to be of the highest consultant standard had he aspired to that end. Although of a quiet and self-effacing nature, he quickly won popularity among a wide circle in Bournemouth, principally from his unfailing kindness. Like so many doctors, he succumbed to the charms of a member of the nursing profession in the person of Miss Anderson, who was at one time on the nursing staff of the Royal Boscombe and West Hants Hospital and later matron of Bodorgan Road War Hospital during the first world war. Perhaps Bottomley's outstanding contribution of voluntary service was for the Order of St. John. He was virtually the founder of the movement in Bournemouth: in the St. John Ambulance Brigade he eventually reached the post of county surgeon for Hampshire, and he was identified with the Bournemouth centre of the St. John Ambulance Association from its inception. Bottomley did strenuous service for the wounded as honorary medical officer to Bodorgan Road War Hospital during the first world war, in addition to his work as physician to Boscombe Hospital, and he, with Mr. Frank Belben, richly deserved their appointment by the King to be Officers of the Order of the British Empire. Many of Bottomley's colleagues have predeceased him, but those who remain will mourn the loss of a reliable friend and a grand Christian gentleman.

G. W. WILL, O.B.E., M.B.

Colonel G. W. Will, editor of the *Journal of the Royal Army Medical Corps* from 1944 to 1950, died on August 15 at the age of 68.

George Wishart Will was born at Oamaru, New Zealand, on October 9, 1885, and was educated at Waitari Boys' High School and Otago University, where he graduated M.B., Ch.B. in 1912. In 1914 he obtained a temporary commission in the R.A.M.C. and served first in France and Belgium, and then with the Rhine Army. He obtained a regular commission in June, 1921. Always interested in psychiatry, he held the Certificate in Mental Diseases granted by the Royal Psychological Society of Great Britain and Ireland, and most of his Service life was spent in practising this specialty. He worked as mental specialist in India (Northern Command) from 1924 until 1929 and at Netley until 1931, when he again embarked for India, serving in the Southern Command until 1937. In the year previous to that his services were recognized by the award of the O.B.E. He returned to Netley and remained there until he was appointed president of the War Office Medical Board at Millbank in 1941, an appointment which he held until his retirement in 1947. In March, 1944, he became editor of the *Journal of the Royal Army Medical Corps*, being succeeded in 1950 by Lieutenant-General Sir Treffry Thompson.

We are indebted to a brother officer for the following appreciation: The passing of George Will brings to an end a valued friendship of some 30 years. I first met him in the early 'twenties when he was a mental specialist, or

"alienist" as we called them in those days. This was, of course, many years before "Army Psychiatry" hit the headlines. The hot weather in India sometimes played strange and alarming tricks with the soldier's brain, and as often as not his visits were in answer to an urgent call to deal with a sudden emergency. Even in those days I have memories of his kindness and courtesy to men of all ranks, his humanity and complete imperturbability, his quiet humour, and, above all, of his shrewd common sense. There was never any vague or woolly diagnosis clothed with jargon or technicalities. His opinions were always clear and concise, and many times he helped to lift a load of responsibility from overburdened shoulders. With the passing of years his fine qualities, matured and developed, made him an outstanding president of the War Office boards. A later generation will remember him during the last 10 years of his life as an ever-popular figure in the mess at Millbank surrounded by friends of all ranks and of all ages. He had an intense love of his Corps, his profession, and his fellow men. It was only given to very few, however, to know of countless acts of kindness unobtrusively given to all sorts and conditions of men, who will join with his friends in mourning his passing and in sympathy with his widow in her grievous loss.

Dr. H. F. L. TAYLOR died at Edinburgh on August 15 at the age of 82 years. The son of the Reverend J. van Someren Taylor, Herbert Francis Lechmere Taylor was born at Dollar, Clackmannanshire, on March 20, 1872, and was educated at George Watson's College and Edinburgh University. After graduating M.B., C.M. in 1896, he very soon afterwards went to the Punjab as a medical missionary of the Church of Scotland, first at Sialkot and later at Jalalpur Jattan. Here, starting out with a capital of some £20, he established and built up a hospital which soon became widely known throughout Northern India for the excellence of its work in general surgery and ophthalmology. His services to India were publicly recognized by the award first of the silver, then of the gold Kaisar-i-Hind medal. In 1905 he returned to Edinburgh to take the D.P.H., and it was not long after this that his book *In the Land of the Five Rivers* was published. Always interested in ophthalmology, he won a gold medal for his thesis on trachoma when proceeding M.D. in 1910. During the first world war he was appointed professor of ophthalmology in the Government Medical College, Lahore, at that time capital of the Punjab, and he served in that capacity for three years. At the end of the war he returned to Scotland and was appointed superintendent and secretary of the Edinburgh Medical Missionary Society. As an integral part of the training for medical missionary students the Society maintained, in the Cowgate, Edinburgh, the Livingstone Memorial Dispensary. This served a wide area of the poorer districts of the city for all medical treatment and was part of the university scheme for dispensary practice in domiciliary medicine and midwifery. It was also a centre for social and evangelistic services. All this medical and Christian social service was under the direct care of Dr. Taylor and was marked by his unfailing enthusiasm and efficiency. At the same time the Society maintained in Damascus, Syria, and in Nazareth, Palestine, two mission hospitals. Dr. Taylor was in charge of the home administration of these hospitals and visited both in the course of his duties, his vast experience of medical missionary work proving of immense value to the Society. During this period he also served as interim-convener of the Foreign Mission Committee of the Church of Scotland, in whose service at a later date he visited the Manchurian mission field as a member of a commission. In 1929, leaving his family in Edinburgh, Dr. Taylor returned to the Punjab for a further term of service in the hospital at Jalalpur Jattan, which was to last for seven years. Once again his wise leadership proved of inestimable value to his colleagues and to the Indian Christian Church. Returning to this country in 1937, he maintained his keen interest in all missionary matters and was ever ready to give freely of his rich experience when called on. During the second world war he rendered valuable service in the medical side of home defence and took an active share in the medical work of the Livingstone Dispensary. His wife, who was a daughter of Mr. Wellesley C. Bailey, worked with him as a medical missionary in India. She died in 1943. Dr. Lechmere Taylor's outstanding ability and gifts of character made a profound impression in every sphere in which he worked—on his patients in hospital, on his missionary colleagues, and, perhaps most of all, on the students preparing to take up medical missionary service. His integrity and self-discipline, the reality of his own Christian faith, and his wise guidance through student years combined to make an indelible impression on all who knew him and who now mourn his passing.—A. M. K.

Dr. C. U. WHITNEY died at his home at Buildwas, Shropshire, on August 6 at the age of 73, and his death deprives the British Medical Association of a loyal and gifted member, his colleagues of an able adviser, and his patients of a family doctor in the best tradition. Cyril Underwood Whitney was born in London on August 19, 1880, and received his medical training at Westminster Hospital, qualifying M.R.C.S., L.R.C.P. in 1910. After acting as assistant house-surgeon and, later, as house-surgeon at Westminster Hospital, he practised in various parts of the country, including West Hoathly, in Sussex, Cradley Heath, in Staffordshire, and Maldon, in Essex, where he was also deputy medical officer of health of the borough and port. During the first world war he was in charge of a Red Cross Hospital at Maldon, and later he served with the R.A.M.C. in Italy. After the war he settled in practice at Iron Bridge, in Shropshire, and there he remained until he moved to the neighbouring village of Buildwas three years ago. His colleagues in Shropshire came to recognize his talents, particularly as a committee man and as a negotiator, and as honorary secretary of the Shropshire local medical and panel committee from 1935 to 1948 he was a familiar figure at many panel and other conferences in London, and his guiding hand was conspicuous in the local discussions leading up to the inauguration of the National Health Service in 1948. He was then the automatic choice as secretary of the new local medical committee, an office he continued to hold until his death. In the affairs of the British Medical Association, too, he took an active part. Becoming a member of the Association immediately after his return from service in the first world war, he was president of the Shropshire and Mid-Wales Branch in 1940–1, and he served as a deputy acting representative at the Annual Representative Meetings at Dublin in 1952 and Cardiff last year. Especially competent in committee work, he had the particular gift of being able to sift the essential from the non-essential, kindly tolerating opposing views and obtaining in the end sensible and unanimous decisions. During the last war he gave valuable assistance at the Red Cross Hospital at Leighton, and up to the time of the inception of the National Health Service he was medical officer of the Lady Forester Hospital, Broseley, and of the Beeches Hospital, Iron Bridge. His was a life of many interests: indeed, wherever an opportunity of useful service to his fellows showed itself, he was prompt to act. The work of the Church was one of his main outside interests, and he became ordained and was an honorary curate in his area of practice. Music, too, keenly appealed to him and he encouraged the activities of glee singers and choirs. He will be greatly missed by his friends, colleagues, and patients, who cannot fail to remember his kindness, his personal interest in them all, and his quiet and reassuring attitude in times of crisis. To his widow and daughter, and to his two sons, who are in practice in the same district, the sympathy of all his friends is extended.—D. A. U.

Dr. J. W. FISHER, who died suddenly on August 16 at his home at Portesham, Dorset, at the early age of 53, was unusual in being a man who had studied science in two diverse

fields, mathematical physics and medicine. Joseph William Fisher studied physics at London University and obtained his B.Sc. with first-class honours in 1921, taking the Ph.D. in 1926. After completion of his university course he studied as a postgraduate at Munich and Göttingen Universities, and on his return spent several years in lecturing and in research work at King's College, London. Not content with this knowledge of the physical sciences, Fisher then turned to medicine and qualified M.R.C.S., L.R.C.P. in 1935. He served for a period at Westminster Hospital as house-physician to the late Dr. David de Souza, and followed this by working as ship surgeon in the Danish ship *Europa* for three months. In 1937 he joined the Anglo-Iranian Oil Company as a member of its geophysical staff, and engaged in research and oil exploration both in this country and in India. In October, 1939, he joined H.M. Underwater Detection Establishment, which is the research establishment of the Admiralty devoted mainly to work on submarine detection. He remained in this service until his death. During these years his brilliant mathematical technique allied to his sure grasp of physical science added much to the fund of knowledge of underwater acoustics. In mathematical analysis he had a flair for seeing the basic problem and that gift for approximation which raises mathematics from a technique to an art. Notwithstanding his mathematical ability, Fisher was a brilliant experimenter and designer of experiments; he was bold in conception where full-scale work was required, but, at the same time, could be just as ingenious with "string and sealing-wax" methods, when he considered that these were adequate to achieve the ends he desired. Withal, Fisher was a great character, with a gift for terse and pithy expression, often coupled with an amusing facility for using analogy based upon his medical experience. His untiring energy and enthusiasm were a continual source of inspiration to those of his colleagues who were privileged to work with him. His death is a great loss to the Royal Naval Scientific Service.—L. R. S.

Dr. DUNCAN MCLELLAN, well known as a general practitioner in Aberdeen, died suddenly after an operation at Leeds on August 27 at the age of 55. It was a coincidence that the news of his death reached Aberdeen on the day his classfellows met to mark the thirtieth anniversary of their graduation. Born on April 2, 1899, Duncan McLellan was the son of Mr. Peter McLellan, of H.M. Customs, and was educated at Perth and at the Nicholson Institute, Stornoway. Like many of his generation, he went straight from school to war service, in his case in the Fife and Forfar Yeomanry and later the Royal Engineers. On demobilization he entered Aberdeen University to study medicine and took an active part in all student activities. After graduating M.B., Ch.B., with distinction, in 1924, he held house appointments at Shrewsbury and Grimsby and at Gateshead, where he set up in practice. He became particularly interested in the treatment of goitre—the surgical work then being done at Newcastle being of absorbing interest—and in 1929 he wrote a thesis on "Clinical Observations and Notes on Some Cases of Goitre," for which he was awarded the M.D. Until 1937 he continued to practise in the north of England and held posts on the staff of the Hospital for Sick Children, Gateshead, and the Ear, Nose, and Throat Hospital, Newcastle. He then returned to the Aberdeen area, and, after a short time at Skene, took up practice in the city and maintained that standard of professional dignity and integrity inculcated in his generation by teachers like the late Sir Ashley W. Mackintosh, professor of medicine at Aberdeen. He took an active part in medical teaching at the dispensary, and during the last war was assistant physician at the Royal Aberdeen Hospital for Sick Children. He died at the height of his powers as a successful practitioner, and will be missed by his patients, whose welfare was always his first care, and by his colleagues, who valued his opinion and advice. He had varied cultural interests in non-professional hours, was a keen gardener and angler, and loved to tell a humorous tale. He married in 1927 Miss Maud S. Morison. The sympathy of all is extended to his widow and son, Dr. Duncan M. McLellan.

Dr. F. E. PRESTON died in a Hampstead nursing-home on August 25 at the age of 66 after a long illness. Francis Edwin Preston was born at Portadown, Co. Armagh, on March 21, 1888, and was educated at Armagh Grammar School and at Dublin, where he took the Irish Conjoint diploma in 1922. He specialized in ophthalmology from the time he qualified, and in 1929 obtained the D.O.M.S. of the English Royal Colleges. He came to England in 1925 and practised at Highgate, Harrow, and Watford before settling at Wanstead in 1929. Among hospital appointments he had held were those of senior house-surgeon at the Western Ophthalmic Hospital and senior clinical assistant at the Royal London Ophthalmic Hospital. For many years he was consulting ophthalmologist to the Jubilee Hospital, Woodford Green, and ophthalmologist to the Wanstead Hospital. He was a past president of the former Association of British Ophthalmologists, and since the introduction of the National Health Service in 1948 had served as a member of the Essex ophthalmic services committee. A member of the British Medical Association for 30 years, he served on the Ophthalmic Group Committee over a long period and he was a member of the special subcommittee on the national eye service. Dr. Preston interested himself in all advances in ophthalmology and spent much time and energy on developing object-tests for children. Owing to failing health in recent years he was unable to produce a second edition of his *Ophthalmic Prescribers' Codex*. He will be much missed by his many friends in Wanstead, where he took an active part in local affairs. He is survived by a widow, a daughter, and two sons, the elder a dental surgeon and the younger a medical practitioner.

Dr. H. W. BOWYER, a much-esteemed general practitioner in Bolton, died suddenly on August 16 while on holiday. He was 53 years of age. Harold Wilson Bowyer was born at Peterculter, Aberdeenshire, on February 5, 1901, and was educated at Whitehill High School in Glasgow and at the University of Glasgow. After graduating M.B., Ch.B. in 1923 he held the appointment of house-surgeon at Glasgow Royal Infirmary, and then worked for a time as a ship surgeon, and at Dukinfield, in Cheshire, before settling in general practice at Bolton early in 1926. He became an honorary anaesthetist at the Bolton Royal Infirmary and physician to the nursing staff, and, being keenly interested in obstetrics, was on the rota of the maternity homes in the district. In 1945, while working as hard as a busy general practitioner must necessarily do, he found the time and the energy to proceed to the M.D., receiving a commendation for his thesis—a significant comment on both his ability and his determination. He worked unstintingly on behalf of his colleagues, holding various offices in the Bolton Division of the British Medical Association. He was honorary secretary of the Division from 1939 to 1945; honorary secretary of the local medical war committee; chairman of the Division 1946 to 1949; and president of the old Lancashire and Cheshire Branch in 1948–9. He also represented the Division at the Annual Representative Meeting on many occasions from 1937 to 1952, and was a member of the General Practice Committee and the Industrial Medical Services Subcommittee for some years. A member of the Bolton Medical Society from 1926 until his death, he was its president in 1949–50. To both his professional duties and his committee work Dr. Bowyer gave unsparing devotion. At the inception of the National Health Service in 1948 he became a part-time consultant physician at Bolton Royal Infirmary, and he also served as a member of medical boards. With little spare time or the leisure for many hobbies, he was nevertheless an enthusiastic golfer when work permitted, and he had been captain of one of the premier clubs in Bolton. As a student he was a keen member of the University's association football club. A member of the Bolton Caledonian Society, he was held in

great esteem by his fellow Scots. The death of a man of his calibre is a loss not only to his immediate family—he leaves a widow, three daughters, and one son—and friends but to the community as a whole, particularly to his patients, to whom he was truly "the beloved physician." As an epitaph one might well say: He was a good man and a wise doctor.—E. P. J.

Mr. M. D. THAKORE writes: Dr. W. W. MCGRATH, whose obituary was printed in the *Journal* of August 21 (p. 475), came to Doncaster Royal Infirmary as house-surgeon to the eye and ear departments early in 1939. After serving his term he went to Gloucester before joining the Forces. In the course of over twenty years as honorary ophthalmic surgeon to the Doncaster Royal Infirmary I have come across many residents appointed to the department. I have no hesitation in recording the fact that Dr. McGrath was among the most efficient, conscientious, and courteous. While in the Forces, and later when in general practice, he kept in touch with me until the end of 1953. While working as an eye specialist in the R.A.F. he told me that his work and experience at Doncaster had helped him considerably in the discharge of his duties, and later he informed me that it was his intention to undertake part-time ophthalmological work when he returned to civilian life. We continued to exchange Christmas greetings up to last year. Hence I read with great sorrow of the passing of such a pleasant colleague in the prime of life. May I convey my sincere sympathy to his family through your esteemed columns?

Universities and Colleges

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At a quarterly comitia of the College held on July 29 with the President, Sir Russell Brain, in the chair, the following Fellows of the College were elected officers for the ensuing year: *Censors*, C. F. T. East, T. C. Hunt, W. E. Lloyd, J. St. C. Elkington; *Treasurer*, W. G. Barnard; *Registrar*, Sir Harold Boldero; *Harveian Librarian*, Sir Charles Dodds; *Assistant Registrar*, M. I. A. Hunter.

Sir Russell Brain was reappointed the College representative on the governing body of the British Postgraduate Medical Federation, and Sir Harold Boldero was elected the College representative on the General Medical Council.

Membership

The following candidates, having satisfied the Censors' Board, were admitted Members of the College:

J. Anderson, M.B., I. S. Bailey, M.B., D. C. G. Bett, B.M., J. D. S. Cameron, M.D., E. D. R. Campbell, B.M., N. Cardoe, M.B., E. H. Cooper, M.B., J. H. Cyriax, M.D., B. M. Davies, B.M., A. M. Dawson, M.B., Stella G. de Silva, L.M.S., J. M. Doyle, M.B., Z. S. Freeman, M.B., J. L. Gibbons, M.B., A. A. Glynn, M.B., H. P. B. Harvey, M.B., J. M. Hinton, M.B., W. H. Jopling, L.R.C.P., J. W. Kerr, M.B., Anne T. Lambie, M.B., F. Lees, M.B., June K. Lloyd, M.B., F. H. Lumb, M.B., J. D. McCreanor, M.B., I. R. McWhinney, M.B., G. C. Manning, M.B., E. A. Martin, M.B., W. M. I. Maxwell, M.B., R. G. May, M.B., J. N. Mickerson, M.D., J. E. Middleton, B.M., B. E. C. Nordin, M.D., J. D. W. Pearce, M.D., C. D. R. Pengelly, M.B., J. I. S. Robertson, M.B., R. Slome, M.D., Jean McI. Smellie, B.M., I. H. Stokoe, M.D., A. R. Stone, M.B., Mary D. Watkins, M.B., R. H. R. White, M.B.

Licences

Licences to practise were conferred upon the following 111 candidates who had passed the final examination in medicine, surgery, and midwifery of the Conjoint Board and who had complied with the by-laws of the College:

R. Allan, A. S. Alvarez, D. A. Ampofo, P. C. Anderson, P. Apali-Oisen, J. Atkins, L. L. Banks, R. G. Bannister, C. J. Barlow, Elizabeth S. M. Barnes, H. N. Baylis, F. Beck, D. A. Bennett, J. G. Bennett, Sheila I. Berry, R. G. Bird, P. W. Blower, W. R. P. Bourne, Patricia M. Boyd, M. J. A. Britten, Daphne J. Broughton, G. R. Brown, R. M. Burton, G. G. Carmichael, R. A. Carpenter, G. Cartmel, J. D. Chard, J. A. Collings-Wells, Anne J. Cour-Palais, Mavis E. Coutts, M. A. Cowan, J. R. Cox, M. C. L. Cox, P. D. Crockatt, R. R. Cundy, E. E. Denman, Doreen J. Dicks, D. Dobson, W. D. Dolton, H. Dovey, P. J. Doyle, E. I. P. Ebosie, C. Ennin, R. C. O. Eruchalu, D. K. Fairweather, P. Y. N. Forget, P. J. Giffard, B. D. Glaisher, N. Gold, G. Gover, G. S. Hall, R. J. Haythornthwaite, P. N. K. Heylings, A. V. Hollingworth, G. Holmes, Rosemary Hulley, J. H. C. Hunt, H. Inceman, D. C. Jackson, J. L. James, A. C. Johansson, D. H. Jones, Beatrice K. Jorgensen, J. D. C. Kelly, G. E. King, N. Landau, T. L. Landau, E. H. Lanford, W. G. R. M. Laurie, L. J. Lawson, N. G. Lewis, Sheila M. Lightowlers, J. L. Loakes, Mary E. Mackintosh, B. H. Markham, D. H. Mathias, M. T. Moore, Margaret Muller, A. F. Munro, R. C. Nainby-Luxmoore, J. D. Nicholas, Margaret B. B. Norcott, W. S. Ogden, Barbara K. Oliver, D. G. Osmond, Margaret R. Palmer, A. M. Parfitt, P. A. P. Pompa, J. B. Pond, A. R. Rizk, B. H. B. Robinson, A. B. Rolfe, D. J. C. Ross, C. A. Rushmer, M. Seigleman, Helen L. Shaw, E. El D. Shoukry, N. A. Silverston, G. W. T. Smith, S. Sochocky], V. E. R. Spence, S. G. Sutton, M. A. Toseland, C. A. M. Walkley, T. J. Walsh, J. Waters, D. N. Whitmore, J. T. N. Williams, P. K. Wilson, S. E. A. Wyner, O. J. Zilliacus.

Diplomas

The following Diplomas were conferred jointly with the Royal College of Surgeons of England:

DIPLOMA IN ANAESTHETICS.—Fiona M. Acheson, Mari Ainsleigh-Jones, J. B. Allan, J. C. T. Archer, S. N. Basu, Khurshid Begum, B. Bhattacharjee, J. H. Birch, B. Blanckenberg, Angela Blundell, F. X. Borg, D. E. Brown, J. A. Burnett, J. D. K. Barton, Lorna Chippindale, E. Cody, A. H. Cohen, Barbara W. Cooke, C. C. Crampton, J. R. Cross, J. Crow, Pauline M. Daniels, A. Danziger, Brenda M. Dempsey, J. R. Duffield, Marjorie J. S. Evans, J. A. Fitzpatrick, Catherine T. Foley, Ellen P. Foley, K. H. Foord, Judith, H. Foote, B. G. Forrest, G. C. Foster-Smith, G. G. France, Margaret Fyfe, N. Garwood, W. S. Hall, J. M. Haughton, B. Hayes, V. M. Hercus, P. J. Horsey, J. G. Hudson, D. C. Hughes, Margaret O. Hunt, A. Hussain, Rosemary Huxley-Williams, C. R. Jolly, K. H. Jooste, Zbigniewa A. Jordan-Sikorska, R. I. Keen, R. King, M. Krausz, A. W. Laing, N. Laurie Smith, J. Lederer, J. Levin, T. J. McCaughey, P. M. F. McGarry, E. L. Magee, Sheila H. Martin, M. D. Mehta, J. A. K. Meldrum, A. J. Merrifield, Rosemary A. Morrell, W. J. Mostert, Agnes P. Muir, P. J. Myles, K. W. Oldham, June M. Oliver, R. M. B. Penhearow, Elizabeth Primrose, Janet P. Rickard, D. G. B. Riddick, P. J. Roffey, Barbara M. Rowe, W. K. Slack, J. W. Smith, Cecily F. Statham, A. R. Sutherland, P. Stuart, V. Subbaraman, J. A. F. Tobin, J. K. Trotter, F. T. G. Tuffnell, Barbara Ward, Alison A. P. Watson, H. N. S. Wilkinson, F. Wilson, B. Wolfson.

DIPLOMA IN CHILD HEALTH.—Elizabeth C. G. Miller,

DIPLOMA IN INDUSTRIAL HEALTH.—S. C. Basu, J. Cameron, J. Chattopadhyay, M. Fitch, G. S. Godiwalla, F. M. James, B. Lall, W. M. McCutcheon, W. S. Millar, P. C. Murray, S. K. Sarkar, J. C. Taylor.

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—D. B. Arnott, C. Aronson, A. K. Bain, J. G. Dickson, M. G. Faruqi, P. W. Head, H. Hirannia, D. C. James, D. W. Khot, Khuan Loon Lam, W. F. Leith, S. D. Mohiuddin, M. A. Qayyum, P. N. Ranade, M. Sen, J. Siegler, R. D. Stride, J. P. Tonkin, G. K. Vincent, N. Vincenti, S. Whitfield.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—C. G. Anderson, D. H. Campbell, P. C. Conlon, R. S. C. Couch, R. I. Green, F. Mulcahy, G. M. Muller, J. B. J. Murray, G. W. Ritchie, P. D. Sutton, A. Woolfson.

DIPLOMA IN MEDICAL RADIOTHERAPY.—H. J. G. Bloom, D. Durbach, H. K. T. Fernando, M. Geoffroy, K. E. Hainan, Barbara A. Hollis, N. T. Nicol, M. J. O'Halloran, E. Sherrah-Davies, Chai-Hee Tsao.

DIPLOMA IN OPHTHALMOLOGY.—Wai Kai Chan, E. C. Cowan, J. F. Cullen, D. H. Dave, M. L. Ghate, S. J. Goddard, A. M. Hasan, D. W. Hill, T. M. M. Hurley, W. A. Hyslop, E. J. McCabe, W. May, H. Mohan, B. D. O'Hanlon, R. E. Onwumere, P. D. G. Quirke, S. D. Sharma, H. P. Spiro, P. N. van Soelen, Zena B. Webster.

DIPLOMA IN PATHOLOGY.—F. G. L. Brafield, K. S. Daber, J. T. Duhig, J. A. Shrigley, R. C. Woodcock.

DIPLOMA IN PHYSICAL MEDICINE.—H. W. Balch, L. P. D. Gunewardene.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—R. W. A. C. Barton, Lorna M. Brierley, Homai M. Colabawalla, A. M. Cook, J. Evans, G. E. Faulkner, Emily M. Frazer, J. G. Gibson, A. W. Griffiths, B. Gupta, R. N. Twistington Higgins, A. R. May, G. A. Nemeth, C. H. Neville-Smith, B. W. Orchard, A. A. Reid, Josephine Rutter, F. G. Tait, J. C. N. Tibbits, J. Todd, J. G. O. Wardell-Yerburgh, M. A. T. Waters, S. Wiseberg.

DIPLOMA IN PUBLIC HEALTH.—J. R. Bhatia, J. F. J. Kelly, J. A. Linden, C. H. Phillips, K. M. Williams, Z. Zubrzycki.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—D. W. Beckett, L. T. Champness, O. F. Conran, S. M. Deoras, M. S. Fardidi, J. Fernandez, S. Ha-Upala, I. Khosla, J. S. Oakey, G. C. Peter, M. Prasad, M. K. Qureshi-ul-Hashmi, H. A. J. Reay, E. S. Reed, C. Siriwann, G. G. Smith, R. M. Vanreenen, K. E. Wardill, A. Werner, J. L. Whitby.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on July 29 with Sir Harry Platt, President, in the chair, the diploma of Fellowship of the College was granted to W. R. O'Flynn, and the diploma of Fellowship of the Faculty of Anaesthetists to G. C. Thick.

Diplomas of Membership of the College, and in Anaesthetics, Child Health, Industrial Health, Laryngology and Otology, Medical Radiodiagnosis, Medical Radiotherapy, Ophthalmology, Pathology, Physical Medicine, Psychological Medicine, Public Health, and Tropical Medicine and Hygiene were granted to the successful candidates whose names are printed above in the report of the meeting of the Royal College of Physicians of London held on July 29.

ROYAL COLLEGE OF SURGEONS IN IRELAND

The following candidates were successful at the postgraduate examinations of the College held during the summer term, 1954:

FINAL FELLOWSHIP.—P. B. Bharucha, P. H. MacAuley.

DIPLOMA IN CHILD HEALTH.—L. S. Devane, B. I. Fitzsimons, G. J. Glynn, J. Heffernan, S. Miller, M. J. McColgan.

DIPLOMA IN ANAESTHETICS.—S. N. Basu, B. Blanckenberg, H. C. Boyd, T. B. Breen, Mary E. Casey, E. Cody, A. H. Cohen, J. A. Fitzpatrick, Margaret T. Kelly, T. J. L'Estrange, Ellen M. Phelan, I. A. Singh, Margaret Timoney, R. D. Walsh.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 21** (No. 33) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954 Eng. & Wales	1954 Lond.	1954 Scot.	1954 N. Ire.	1954 Eire	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire
Diphtheria	8	0	4	0	0	11	0	6	1	1
Dysentery	390	57	160	1	1	334	35	84	1	
Encephalitis, acute	3	1	0	0		5	0	0	0	
Enteric fever: Typhoid	6	0	1	2	0	4	1	0	0	1
Paratyphoid	21	0	2	0	11 (B)	19	2	2	0	4
Food-poisoning	175	13		0	0	769	169		0	
Infective enteritis or diarrhoea under 2 years				21	12				13	46
Measles*	2,255	105	40	38	60	3,587	80	83	83	82
Meningococcal infection	16	2	11	0	1	21	2	12	2	
Ophthalmia neonatorum	31	1	7	1		37	4	4	0	
Pneumonia†	225	14	62	1	1	222	11	99	0	
Poliomyelitis, acute: Paralytic	55	3	15	2	2	167	22	13	18	10
Non-paralytic	34	8				103	12			
Puerperal fever§	230	42	12	2	0	232	18	5	0	
Scarlet fever	379	27	72	10	23	950	55	97	20	31
Tuberculosis: Respiratory	677	64	103	13				129	32	
Non-respiratory	113	9	18	3				32	2	
Whooping-cough	1,942	100	156	43	26	4,107	347	369	55	37

DEATHS in Great Towns	1954 Eng. & Wales	1954 Lond.	1954 Scot.	1954 N. Ire.	1954 Eire	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire
Diphtheria	0	0	0	0	0	2	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	1	0	1	5	1	1	1	2
Influenza	2	0	1	0	0	3	1	0	0	0
Measles		0	0	0	0		0	0	1	0
Meningococcal infection		0	0				1	0		
Pneumonia	137	19	11	5	3	117	12	6	3	5
Poliomyelitis, acute	4	0			0	10	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis: Respiratory	59	4	8	0	5	85	13	10	1	3
Non-respiratory		1	10	0	1		1	1	0	0
Whooping-cough	1	0	1	0	0	5	1	0	0	1
Deaths 0–1 year	170	19	20	4	7	201	30	24	9	13
Deaths (excluding stillbirths)	4,286	622	485	82	121	4,284	590	455	87	130
LIVE BIRTHS	7,236	1124	889	197	341	7,974	1204	921	230	395
STILLBIRTHS	184	21	27			187	21	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

A decline occurred in the incidence of most infectious diseases in England and Wales during the week ending August 21. The falls in the number of notifications included 585 for measles, from 2,840 to 2,255, 148 for whooping-cough, from 2,090 to 1,942, 54 for acute pneumonia, from 279 to 225, and 52 for scarlet fever, from 431 to 379.

The number of notifications of scarlet fever were the lowest recorded and were 52 below the lowest level of 1953. The largest decline during the week reviewed was 22 in Yorkshire West Riding, from 57 to 35. The largest declines in the incidence of measles were 163 in Lancashire, from 635 to 472, 143 in Cheshire, from 356 to 213, and 60 in Durham, from 364 to 304. 8 cases of diphtheria were notified, 1 more than in the preceding week. 3 of the cases were notified in Birmingham C.B. The largest falls in the number of notifications of whooping-cough were 35 in Nottinghamshire, from 114 to 79, and 33 in Durham, from 126 to 93.

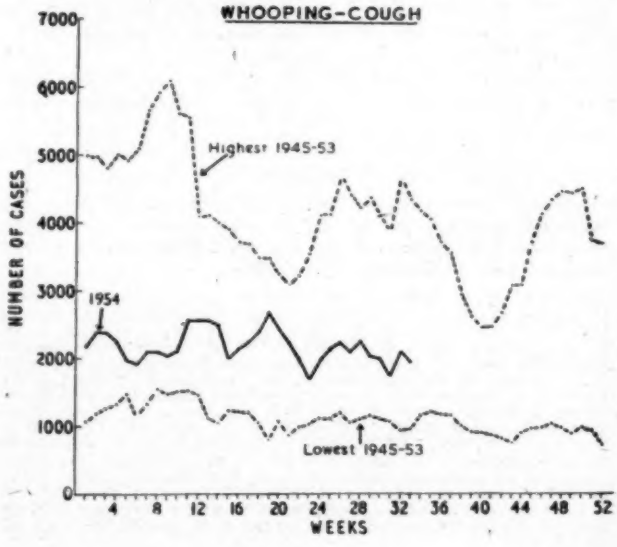
The largest outbreaks of paratyphoid fever were Yorkshire West Riding, Queensbury and Shelf U.D. 5, and Lincolnshire, Bourne U.D. 4.

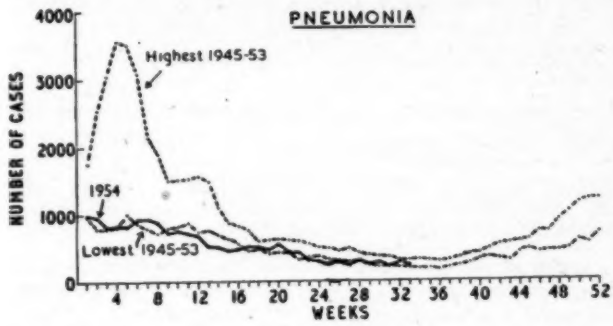
89 cases of acute poliomyelitis were notified. These cases were 5 fewer for paralytic and 3 fewer for non-paralytic cases than in the preceding week. The largest returns were London 11 (Islington 3, Lewisham 2), Yorkshire East Riding 8 (Kingston-upon-Hull C.B. 3, Beverley M.B. 2), Lancashire 7 (Liverpool C.B. 2), Yorkshire West Riding 6 (Leeds C.B. 3), Durham 5 (Gateshead C.B. 3), and Sussex 5.

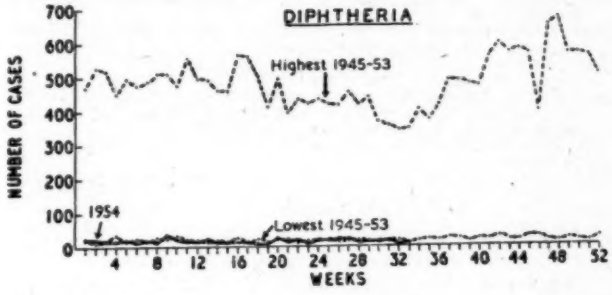
390 cases of dysentery, 6 more than in the preceding week, were notified. The largest returns were Lancashire 79 (Manchester C.B. 25, Liverpool C.B. 23), London 57 (Islington 14, St. Pancras 13), Yorkshire West Riding 54 (Leeds C.B. 12, Sheffield C.B. 10), Durham 46 (Hebburn U.D. 44), and Lincolnshire 17 (Boston M.B. 10).

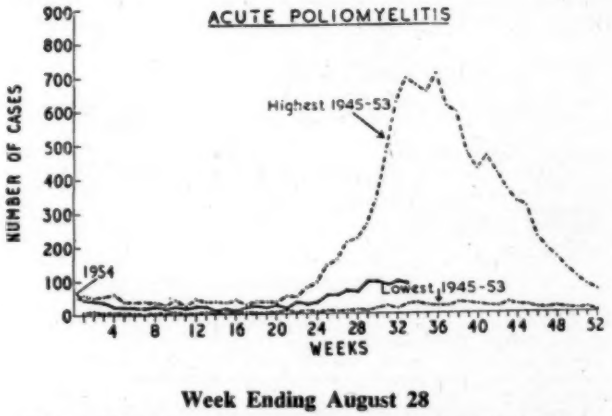
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending August 28

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 349, whooping-cough 2,038, diphtheria 4, measles 1,699, acute pneumonia 217, acute poliomyelitis 79, dysentery 341, paratyphoid fever 8, and typhoid fever 1.

Medical News

Visit to Russia.—A party of doctors left London on September 3 for a three-weeks visit to Russia, under the auspices of the medical section of the Society for Cultural Relations with the U.S.S.R. The party consists of: Lord AMULREE, physician, University College Hospital, London, and president of the Medical Society for the Care of the Elderly; Dr. C. A. BIRCH, physician, Chase Farm Hospital; Mr. A. R. CLARKE, surgeon, Birmingham Accident Hospital; Dr. ALEX COMFORT, Nuffield research assistant, Biology of Old Age, University College, London; Dr. L. CROME, neuropathologist, Fountain Hospital, London; Dr. T. D. CULBERT, anaesthetist, United Manchester Hospitals; Dr. F. A. ELLIOTT, assistant physician, Charing Cross Hospital; Dr. SARAH FISHER, general practitioner, London; Dr. T. F. FOX, Editor of the *Lancet*; Mr. A. W. L. KESSEL, orthopaedic surgeon, Fulham and Kensington Hospitals Group; Professor ESTHER KILLICK, professor of physiology, London University; Dr. HELEN MAIR, assistant medical officer, Maternity and Child Welfare Department, Manchester; Dr. N. B. MALLESON, physician in charge of Student Health Association, University College, London; Dr. J. G. OLLERENSHAW, general practitioner, Skipton, Yorkshire; Mr. R. ROAF, orthopaedic surgeon, Royal Liverpool United Hospitals; Dr. C. H. C. TOUSSAINT, chest physician, Central Middlesex Hospital, and vice-president, British Tuberculosis Association; and Dr. L. R. WEST, medical officer, Sully Hospital, Glamorgan. There are two non-medical members, Mr. E. G. BRAITHWAITE, secretary of the South-western Metropolitan Regional Hospital Board, and Dr. M. ABERCROMBIE, reader in embryology, University College, London.

Rockefeller Grants.—Medical projects figure prominently in the quarterly list of Rockefeller Foundation grants just published (Second Quarter, 1954). On this occasion the major benefactions to medicine go to American institutions. Harvard Medical School gets $275,000 for the development of a family treatment plan: this is a scheme to enable medical students to follow their patients from home to hospital and back again. The National Research Council's committee on sex research gets further aid, in the form of a three-year grant of $150,000. In the past this committee has supported investigations as diverse as the isolation of sex hormones and Dr. ALFRED KINSEY'S studies on human behaviour. A new grant of $150,000 brings the total amount given to National Research Council fellowships in medical sciences to the high level of $1.7 million. These fellowships have been awarded continuously since 1924. The Rockefeller Foundation stresses their special value in that the recipient is not restricted in his choice of subject or place of study. Although medical fellowships are now far more numerous than formerly, many are restrictive; the N.R.C. fellowships are designed "to counteract the trend towards rigidity." Other large grants go towards virus research (California and Washington); studies on insect resistance to D.D.T. (Illinois), genetics (Texas), and the relationship between schizophrenia and the adrenal glands (Saskatchewan); and to support the Department of Psychiatry at McGill. In Britain Dr. H. A. KREBS, F.R.S., the Nobel laureate, receives a grant of $80,000 for his studies on cell metabolism, and King's College, Durham, £16,000 towards its expanded programme of training West Africans in public health engineering. Other grants go to Professor J. T. RANDALL, F.R.S., at King's College, London ($6,000 for research in biophysics); Dr. J. N. MORRIS, director of the M.R.C. Social Medicine Research Unit ($1,150 to visit the U.S.A.); Dr. J. F. TAIT, Middlesex Hospital Medical School ($1,100 to visit the U.S.A. and Canada); Dr. T. W. GOODWIN, Liverpool University ($1,200 to visit the U.S.A.); and Miss M. B. POWELL, matron of St. George's Hospital, London ($1,700 to visit North America).

The Collegium Oto-Rhino-Laryngologicum.—During its meeting in London the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum held a banquet in the Great Hall of B.M.A. House on August 31, when the president of the Collegium, Mr. V. E. NEGUS, was in the chair. Among the guests were the President of the B.M.A., Sir JOHN MCNEE, with Lady MCNEE, and the Chairman of Council, Dr. E. A. GREGG, with Miss GREGG. The hall was filled with oto-laryngologists from many countries and their wives. After the loyal toast had been honoured the health of "The Heads of the Countries represented at the Meeting" was drunk. After Sir JOHN MCNEE had toasted "The Collegium" responses were made by Professor E. HUIZINGA, of Holland, Professor G. PORTMANN, of France, Professor H. FRENZEL, of Germany, Professor G. FERRERI, of Italy, Dr. A. N. PROETZ, of the U.S.A., and Professor C. O. NYLEN, of Sweden.

Television and Children.—The Nuffield Foundation is sponsoring a two-year investigation into the effects of television on children and young people in Britain. The work will be done by a team led by Dr. HILDE HIMMELWEIT, reader in social psychology at the London School of Economics. A steering committee, with Sir HECTOR HETHERINGTON, Principal of Glasgow University, as chairman, has been appointed to assist her. Professor J. Z. YOUNG, F.R.S.,

Department of Anatomy and Embryology, University College, London, is a member of the committee. There are three psychologists on the committee, but no medical men.

Slum Clearance.—Local authorities in England and Wales have been asked by Mr. HAROLD MACMILLAN, Minister of Housing and Local Government, to send their slum clearance proposals to him by August 30 next year for his approval. In a circular Mr. Macmillan says that in examining proposals he "will require to be satisfied that these provide for the solution of the slum problem as quickly as the council's commitments and resources, and the supplies of building labour and materials, permit."

Journal Index.—The half-yearly indexes to Volume I of the *Journal* and the *Supplement* for 1954 are now being sent to members who receive them regularly and to subscribers. Members who have not previously asked for the indexes to be sent regularly to them can obtain copies, post free, on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1; those wishing to receive the indexes regularly as published should mention this.

Van Meter Prize.—The American Goiter Association is offering a prize of 300 dollars and two honourable mentions for the best essays on original work (clinical or laboratory) on problems related to the thyroid gland. Essays should not be more than 3,000 words in length. Details from the Secretary, Dr. JOHN C. MCCLINTOCK, 149½, Washington Avenue, Albany, New York.

Sir Harry Platt, P.R.C.S., received the honorary degree of Doctor of Medicine of Berne University on August 30, at the inaugural meeting of the 6th Congress of the International Society of Orthopaedic Surgery and Traumatology.

COMING EVENTS

The London Medical Exhibition will be held on November 15 to 19 at the Royal Horticultural Hall, Westminster, *not* in September as stated in last week's issue (p. 604). Tickets from British and Colonial Druggist Ltd., 194, Bishopsgate, London, E.C.2.

Myxomatosis.—Background information about the spread of myxomatosis and its economic and moral implications, prepared by R. M. LOCKLEY, will be broadcast on the Home Service at 7.15 p.m. on Tuesday, September 14.

Fédération Internationale Pharmaceutique.—The 16th General Assembly will be held in London next year (September 19 to 23, 1955). The Pharmaceutical Society of Great Britain is making the arrangements.

Association of Clinical Pathologists.—53rd General Meeting at Brighton, September 30 to October 2. Hon. Secretary: Dr. W. H. MCMENEMEY, Maida Vale Hospital for Nervous Diseases, London, W.9.

Manson Lecture.—Sir PHILIP MANSON-BAHR will deliver the Manson Lecture at 5.15 p.m. on October 5 at the London School of Hygiene and Tropical Medicine. His subject will be "Patrick Manson: the Father of Tropical Medicine and the Founder of the School of Tropical Medicine."

Nutrition Society: Scottish Group.—Symposium on "Disorders of the Alimentary Tract and their Nutritional Effects" at Dundee, October 23. Details from Professor R. B. HUNTER, Department of Pharmacology and Therapeutics, The Medical School, Queen's College, Dundee.

NEW ISSUES

Abstracts of World Medicine.—The September issue (Vol. 16, No. 3), which is now available, contains abstracts of important papers drawn from medical and other scientific journals published in some 20 different countries and in all five continents. The subjects covered range over the whole field of clinical medicine and include pathology, bacteriology, pharmacology, and chemotherapy; there are also sections dealing with medical genetics, public health and industrial medicine, forensic medicine and toxicology, anaesthetics, radiology, and the history of medicine.

Issued monthly; annual subscription £4 4s.; single copy 8s. 6d.; a specimen will be sent free on request.

Medical and Biological Illustration.—The new issue (Vol. IV, No. 3) will be available in a week's time. The contents include:

SOME DEVELOPMENTS WITH LOW-ENERGY GAMMA-RAY SOURCES. JULES GERMAIN CLOQUET. W. J. Bishop.
ILLUSTRATION FOR MEDICINE. C. W. Dixon and H. G. Lumby.
PROBLEMS IN BIOLOGICAL ILLUSTRATION. E. R. Turlington and Jane de Vere.
ASSESSMENT OF SPINAL MOVEMENT. James Kilshaw and Robert Ollerenshaw.
PLASTIC CONTAINERS FOR MUSEUM SPECIMENS. J. E. Morton.
EQUIPMENT AND METHODS.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Annals of the Rheumatic Diseases.—The new issue (Vol. 13, No. 3) will be available in a week's time. The contents include:

ANKYLOSING SPONDYLITIS: A SURVEY. F. Dudley Hart.
HISTORY OF THE USE OF COLCHICUM AND RELATED MEDICAMENTS IN GOUT. Edward F. Hartung.
ZONE ELECTROPHORETIC STUDIES OF PLASMA PROTEINS IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS. T. E. Hunt and J. A. Trew.
COMPLEMENTARY ACTIVITY OF THE BLOOD IN RHEUMATISM AND CERTAIN ALLIED DISORDERS. C. E. Kellett.
HISTOLOGICAL STUDIES OF PELVO-SPONDYLITIS OSSIFICANS (ANKYLOSING SPONDYLITIS) CORRELATED WITH CLINICAL AND RADIOLOGICAL FINDINGS. Bengt Engfeldt, Ragnar Romanus, and Sven Yden.
RARE FEATURES IN A CASE OF GAUCHER'S DISEASE. E. Adler and S. Maybaum.
SODIUM SALICYLATE AND PROBENECID IN THE TREATMENT OF CHRONIC GOUT. F. G. W. Marson.
ANATOMICAL CONSIDERATIONS IN INJECTION OF THE HIP JOINT. J. M. F. Landsmeer and A. K. J. Koumans.
EFFECT OF THYROIDECTOMY IN RHEUMATOID ARTHRITIS. Veikko A. I. Laine, Kauko J. Vainio, and T. E. Holopainen.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, September 14

EDINBURGH UNIVERSITY: FACULTY OF MEDICINE.—At West Lecture Theatre, University New Buildings, Teviot Place, 5 p.m., Macarthur Postgraduate Lecture by Professor J. P. Hoet (Louvain): Pre-Diabetic State as Exemplified by Pregnancy.

APPOINTMENTS

LAWSON, T. O. P. D., M.D., D.P.H., D.R.C.O.G., Medical Officer of Health and School Medical Officer, Borough of Cheltenham, and Divisional Medical Officer, Gloucestershire County Council.

METHVEN, JAMES BLACK, M.B., Ch.B.Ed., D.Psych., Consultant Psychiatrist and Physician Superintendent, Royal Scottish National Institution, Larbert, Stirlingshire.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—G. W. S. Andrews, M.B., B.S., Consultant Pathologist, Mount Vernon Hospital, Northwood; J. D. O'D. Lavertine, M.D., Consultant in Morbid Anatomy, Hillingdon Hospital, Uxbridge; D. W. Bain, F.R.C.S., Consultant General Surgeon, King Edward VII Hospital, Windsor, and Maidenhead Hospital; C. W. A. Searle, M.D., D.O.M.S., Consultant Ophthalmologist, St. Charles's Hospital, Ladbroke Grove, W.; C. A. Storr, M.B., M.R.C.P., D.P.M., Assistant Psychiatrist (S.H.M.O.), West End Hospital for Nervous Diseases; Margaret Ford, M.B., Ch.B., D.O., Assistant Ophthalmologist (S.H.M.O.), School Eye Clinic, King Edward VII Hospital, Windsor.

WALDRON, D. H., M.D., D.P.H., D.T.M.&H., Colonel, I.M.S.(ret.), Medical Officer of Health, Buckingham Borough, Bletchley Urban District Council, Linslade Urban District Council, Newport Pagnell Urban District Council, Buckingham Rural District Council, Wing Rural District Council, Newport Pagnell Rural District Council, and Area Medical Officer, North Buckinghamshire.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Watson.—On August 5, 1954, to Dr. Barbara (formerly Leach), M.B., B.Ch., wife of D. A. Watson, B.A., M.R.C.V.S., of 18, Denmark Road, Gloucester, a brother for Sally-Ann.

DEATHS

Martin.—On August 24, 1954, at Llandough Hospital, near Penarth, Glamorganshire, Allan Martin, M.D., D.P.H., of 133, Cyncoed Road, Cardiff.

Martin.—On August 25, 1954, James Sackville Martin, M.D., of 73, Hillsboro Road, Bognor Regis, Sussex, late of Leigh, Lancashire.

Nicol.—On August 26, 1954, at 18, Christchurch Hill, Hampstead, London, N.W., Hamish Nicol, F.R.C.S.Ed.

Scowby.—On August 9, 1954, at Preston, Lancs, Edward Thomas Scowby, M.B.

Unsworth.—On July 30, 1954, at "Hilbre," Sutton, St. Helens, Lancs, John Unsworth, M.B., Ch.B., aged 51.

West-Watson.—On February 5, 1954, killed while on duty in the Alaska plane disaster, William Ronald West West-Watson, M.B.E., M.B., B.S., Lieutenant-Colonel, R.A.M.C.

Witney.—On August 21, 1954, Ernest William Witney, M.B., B.S., of White Croft, Whitstable, Kent.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Penicillin Dosage

Q.—*(a) What is the current opinion on dosage and frequency of administration of crystalline penicillin in susceptible infections, excluding subacute bacterial endocarditis? (b) In treating non-tuberculous infections with streptomycin is there any advantage in giving 0.5 g. twice daily over giving 1.0 g. daily?*

A.—(*a*) The first of these questions is one which has been debated for years, and about which there is still no general agreement. The alternatives are to give large doses at long intervals, which produce at first a very high concentration in the blood which disappears some hours before another dose is given, or to give smaller doses more frequently. The advantage of the former method is claimed to be that when the blood concentration is high the drug diffuses better into a closed focus of infection: it also remains there longer than it does in the blood. This is undoubtedly true when a closed focus exists, such as an abscess or effusion. A better alternative when such a lesion is large and accessible may be either drainage or the injection of penicillin directly into it. On the other hand, it has been shown not to be true of acute inflammation in an area well supplied with blood, where no tissue breakdown has occurred—for example, acute streptococcal myositis in mice.[1] The advantage of smaller doses at shorter intervals is that a continuous effect can thus be secured: there is a good deal of evidence that this is more certainly curative than an "intermittent" schedule, and certainly none that it can ever be less so. The most comprehensive experiments on this subject, which afford a rational basis for systems of treatment, are those of Eagle *et al.*[2] As direct practical advice it may be said that either 500,000 units at 12-hour intervals, or 100,000 at 4- or 5-hour intervals should produce a satisfactory effect in fully susceptible infections, but it must be remembered that susceptibility to penicillin is very variable even among bacteria usually classed as sensitive, and the situation, extent, and seriousness of the infection must also be taken into account in deciding dosage. That subacute bacterial endocarditis is not the only exceptional condition will be evident from the mention of, for instance, pneumococcal meningitis and gas gangrene.

(*b*) The efficacy of infrequent doses of streptomycin in tuberculosis is something exceptional, and has no parallel in other infections. For such a condition as a non-tuberculous urinary infection, streptomycin should be given not once or twice, but three times a day: only a brief period of treatment is necessary. If bacterial recovery is permitted between one dose and the next, acquired resistance is very likely to develop and treatment will then fail.

REFERENCES

[1] Eagle, H., *et al.* (1950). *J. Bact.*, **59**, 625.
[2] *New Engl. J. Med.*, 1953, **248**, 481.

Tropical Ear

Q.—*What is the aetiology of tropical ear? How should the condition be treated?*

A.—Bacterial and fungal infections of the skin are more prevalent, troublesome, and persistent in hot climates than in cold, as the skin there is moist. In the Tropics the external auditory meatus is not uncommonly involved in such infections, and names like tropical ear, hot weather ear, Singapore or Hong Kong ear have been loosely applied. Probably most commonly the infection is primarily a bacterial one, and a saprophytic fungal infection is superimposed on it. Alternatively, the infection may primarily be a fungal one which is complicated by secondary bacterial infection. The fungi associated with otomycosis are numerous, but those belonging to the genera *Aspergillus, Penicillia, Mucoracaea,* and *Candida* are said to be the most common, the first of these greatly predominating. Cultural studies are necessary to identify them. The first aim is to dry the ear. It should be cleansed by carefully swabbing, and before embarking on any further treatment it is well to ensure that the drum is intact. Local inflammation should be treated by suitable means. Antibacterial and symptomatic treatment consists of irrigation with 50% hydrogen peroxide to remove exudate and detritus. Aqueous gentian violet in 1% solution or 2% aqueous silver nitrate may then be applied. The fungicides recommended for use in the meatus are metacresylacetate 1/1,000 or thymol 1–2% in 70% alcoholic solution. The latter causes stinging. After drying by swabbing, the ear may be packed with absorbent cotton moistened in the solution of metacresylacetate; this pack is removed the following day, and six drops of the thymol solution are then introduced twice daily for five days. Thymol iodide powder may then be insufflated into the ear for another five days. In very persistent cases fractional *x*-ray therapy may be necessary.

Itching in Hodgkin's Disease

Q.—*I would be grateful if you could offer me any suggestions for the treatment of intense itching in a patient with advanced Hodgkin's disease. Sedatives and antihistamines have been tried without success.*

A.—When itching occurs in leukaemia and Hodgkin's disease, it is notoriously intractable. It is possibly a reaction to protein breakdown products from the affected tissues, and it is therefore worth trying treatment with A.C.T.H. or cortisone, which are often successful in other cutaneous manifestations of these diseases. Methyl testosterone has recently been reported to relieve the itching of jaundice; its mode of action is unknown, but it again would be worth trying in this case.

Eggs from Battery Hens

Q.—*I am told that eggs produced by the battery method have pale coloured yolks and lack taste, and also that hens kept in deep litter tend to turn cannibal. Both these facts might indicate some food deficiency. Has any work been done on the relative food value (including, of course, vitamin content) of eggs produced in these ways, compared with those produced under the "old-fashioned" but more natural conditions?*

A.—The depth of yellow colour in egg yolks is increased in relation to the amounts of xanthophylls which are present in the diet, and decreased in relation to the speed at which eggs are laid. Pale eggs will be produced, therefore, irrespective of the method of management when eggs are being laid freely and the food is low in xanthophylls. If the diet for hens kept in a battery contains adequate amounts of yellow maize or fresh or dried green vegetable matter, the production of eggs with pale yolks can doubtless be avoided. The taste of the eggs will also depend on the diet. Too much cod-liver oil, for example, will give a fishy taste irrespective of the method of management. Cannibalism is not confined to hens kept on deep litter, and the popularity of this procedure suggests that it does not occur very often. Progress in poultry research institutes is intense, and it would be rash to state that no comparisons of eggs produced by the old and new methods have yet been made. If such research has been done, however, the results are not yet widely known. Any investigation, of course, would have to take into account the possibility of wide variations in the diet under both the new and "old-fashioned" methods of management.